

# Evolution of a Synthetic Strategy: Total Synthesis of (±)-Welwitindolinone A Isonitrile.

Sarah E. Reisman, Joseph M. Ready, Matthew M. Weiss, Atsushi Hasuoka, Makoto Hirata,  
Kazuhiko Tamaki, Timo V. Ovaska, Catherine J. Smith and John L. Wood<sup>†\*</sup>

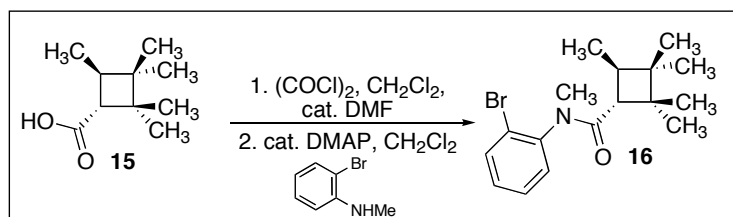
*Contribution from Sterling Chemistry Laboratory, Department of Chemistry, Yale University,  
New Haven, CT 06520-8107*

john.l.wood@colostate.edu

**Supporting Information 1 (Experimental Procedures):**

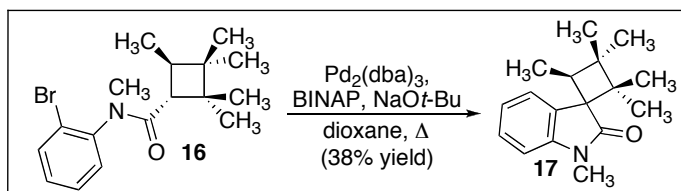
**General.** Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF) was dried either by distillation from sodium/benzophenone or by passing through activated alumina columns. Methylene chloride ( $\text{CH}_2\text{Cl}_2$ ), diethyl ether ( $\text{Et}_2\text{O}$ ), and acetonitrile (MeCN) were dried by passing through activated alumina columns. Dimethylformamide (DMF) was dried over activated molecular sieves, and MeOH was distilled over magnesium oxide. All other commercially obtained reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (partical size 0.032-0.063) purchased from Silicycle. Microwave experiments were performed using a Biotage Initiator® microwave reactor.  $^1\text{H}$  NMR spectra were recorded at 500 MHz or 400 MHz using a Bruker AM-500, Bruker Avance DPX-500 or Bruker AM-400 instrument.  $^{13}\text{C}$  NMR spectra were recorded at 126 MHz or 100 MHz using a Bruker AM-500, Bruker Avance DPX-500 or Bruker AM-400 instrument. Chemical shifts are reported relative to internal chloroform ( $^1\text{H}$ ,  $\delta = 7.26$ ,  $^{13}\text{C}$ ,  $\delta = 77.2$ ), dimethyl sulfoxide ( $^1\text{H}$ ,  $\delta = 2.50$ ,  $^{13}\text{C}$ ,  $\delta = 40.3$ ), methanol ( $^1\text{H}$ ,  $\delta = 3.31$ ,  $^{13}\text{C}$ ,  $\delta = 49.0$ ) or methylene chloride ( $^1\text{H}$ ,  $\delta = 5.32$ ,  $^{13}\text{C}$ ,  $\delta = 54.0$ ) as indicated. Infrared spectra were recorded on a Midac M-1200 FTIR. Melting points were obtained on a Gallenkamp variable temperature melting point apparatus and are uncorrected. Low-resolution mass spectra were acquired on a Waters Micromass® ZQ instrument using electrospray ionization (EI). High-resolution mass spectra were acquired at the University of Illinois Mass Spectrometry Center.

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra are included for all previously unreported compounds.



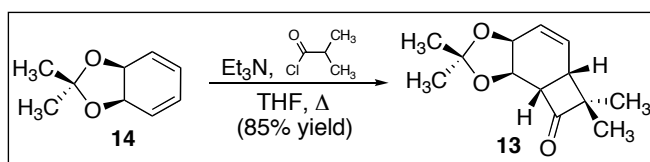
**Anilide 16.** To a solution of 2,2,3,3,4-pentamethylcyclobutane-1-carboxylic acid (**15**) (90 mg, 0.53 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added oxalyl chloride (69  $\mu\text{L}$ , 0.79 mmol, 1.5 equiv) followed by a catalytic amount of DMF (2  $\mu\text{L}$ ), which resulted in the immediate evolution of gas. The resulting solution was allowed to stir for 30 min before being concentrated under reduced

pressure. The derived residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and cooled to 0 °C before a solution of *N*-methyl-2-bromoaniline (130 mg, 0.69 mmol, 1.3 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added dropwise. A catalytic amount of DMAP (1 mg) was added and the reaction was allowed to slowly warm to room temperature and stir overnight. The mixture was absorbed onto silica gel and subjected to flash chromatography (20% EtOAc/hexanes eluent) to afford anilide **16** (170 mg, 94% yield) as a white solid. m.p. 79-80 °C; FTIR (thin film/NaCl) 2956 (s), 2868 (w), 1661 (s), 1474 (s), 1418 (m), 1367 (w), 1278 (w), 1142 (w), 1025 (w), 764 (w), 730 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.67-7.64 (m, 2H), 7.39-7.34 (m, 2H), 7.24-7.17 (m, 4H), 3.20 (s, 3H), 3.17 (s, 3H), 2.59-2.45 (m, 2H), 2.39 (d, *J* = 10.2 Hz, 1H), 2.12 (d, *J* = 10.0 Hz, 1H), 1.03 (s, 3H), 0.99 (s, 3H), 0.80-0.76 (m, 12H), 0.67 (s, 3H), 0.66 (s, 3H), 0.49 (s, 3H), 0.48 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.2, 172.0, 142.8, 142.6, 133.9, 133.6, 131.2, 130.7, 129.5, 129.3, 128.5, 128.4, 123.8, 123.7, 51.7, 50.8, 41.9, 41.5, 38.4, 37.1, 36.9, 36.1, 36.0, 24.0, 23.4, 23.1, 23.0, 21.2, 20.3, 19.7, 19.6, 12.9, 12.6; HRMS (EI) calc'd for C<sub>17</sub>H<sub>24</sub>BrNO [M<sup>+</sup>] 337.1041, found 337.1038.



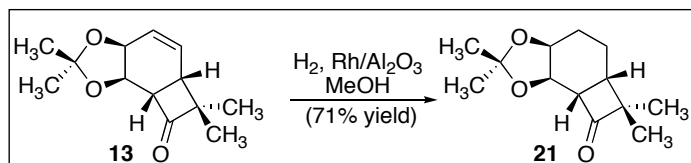
**Preparation of Oxindole 17.** A flame dried flask was charged with Pd<sub>2</sub>(dba)<sub>3</sub> (27 mg, 0.03 mmol, 0.10 eq.), BINAP (18 mg, 0.03 mmol, 0.10 eq.), and *t*-BuONa (36 mg, 0.44 mmol, 1.5 eq.). The flask was then evacuated and kept under high vac. for 30 min. After backfilling the flask with nitrogen, freshly distilled dioxane (3mL) was introduced to provide a deep red suspension. This suspension was then degassed by three repeated cycles of evacuating the flask and then backfilling it with nitrogen. A solution of amide **16** (100 mg, 0.30 mmol, 1.0 equiv) in freshly distilled dioxane (3 mL) was then introduced into the flask via syringe. The resulting red suspension was then immersed in an oil bath preheated to 110 °C. Over a period of three h, the red suspension gradually faded in color and ultimately turned into a pale yellow suspension. The reaction was heated in dioxane for a total of 12 h, at which point TLC indicated the complete

consumption of starting material and formation of higher  $R_f$  products. The reaction was removed from the oil bath cooled to room temperature before dilution with  $\text{Et}_2\text{O}$  (10 mL) and poured into saturated  $\text{NH}_4\text{Cl}$  (15 mL). The layers were separated and the aqueous layer was extracted with  $\text{Et}_2\text{O}$  (3 x 10 mL). The combined organic layers were washed with brine and dried over  $\text{MgSO}_4$ . Concentration followed by absorption of the derived residue on silica gel was followed by flash chromatography (30%  $\text{EtOAc}$ /hexanes eluent) to furnish oxindole **17** (29 mg, 38% yield) as a white solid. m.p. 121.5-123.5 °C; FTIR 2950 (m), 2925 (m), 1697 (s), 1611 (m), 1475 (w), 1345 (w), 1092 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (d,  $J = 7.3$  Hz, 1H), 7.23 (dt,  $J = 1.5$ , 7.8 Hz, 1H), 7.03 (dt,  $J = 1.0$ , 7.5 Hz, 1H), 6.73 (d,  $J = 7.8$  Hz, 1H), 3.14 (s, 3H), 2.63 (q,  $J = 7.0$  Hz, 1H), 1.38 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H), 0.98 (s, 3H), 0.87 (d,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  177.5, 144.1, 130.0, 127.2, 125.0, 121.0, 106.9, 58.3, 44.5, 43.5, 38.4, 25.7, 25.6, 24.8, 20.3, 19.1, 8.5; HRMS (EI) calc'd for  $\text{C}_{17}\text{H}_{23}\text{NO}$  [ $\text{M}^+$ ] 257.1780, found 257.1778.

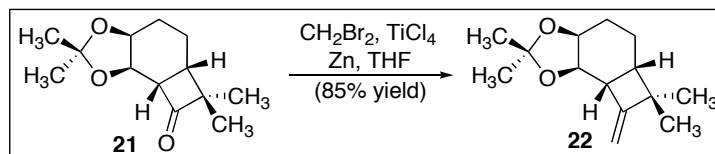


**Preparation of Cyclobutanone 13.** A solution of diene **14** (8.22 g, 54.1 mmol, 1.0 eq.) and  $\text{Et}_3\text{N}$  (54.0 mL, 387 mmol, 7.1 equiv) in THF (210 mL) was brought to reflux and maintained at this temperature while isobutyryl chloride (40.0 mL, 382 mmol, 7.1 equiv) was introduced over a period of 15 h. Immediately upon the addition of isobutyryl chloride a white precipitate began to form. The mixture was allowed to reflux for an additional 12 h before the reaction was cooled to room temperature and filtered to remove the triethylamine hydrochloride salt. The solution was then concentrated under reduced pressure (rotary evaporator) keeping the temperature under 10 °C to provide an orange oil containing a large amount of a white precipitate. To this mixture was added 750 mL of a 20%  $\text{EtOAc}$ /hexanes solution. Following removal of approximately half of this volume under reduced pressure, an additional 300 mL of hexanes was introduced and the mixture was filtered to remove the white precipitate, which consisted entirely of 2,2,4,4-

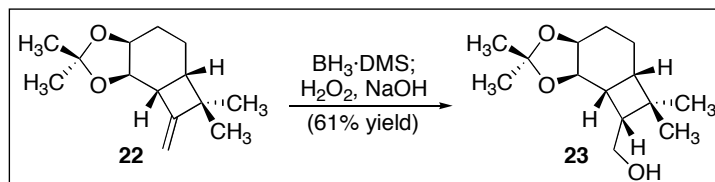
tetramethyl-cyclobutane-1,3-dione, resulting from the dimerization of dimethyl diketene. This precipitate was washed well with hexanes, and the resulting filtrate was concentrated. The resulting residue was subjected to silica gel chromatography (2-10% EtOAc/hexanes eluent) to provide cyclobutanone **13** (10.21 g, 85% yield) as a white solid. m.p. 93.5-95.5 °C; FTIR (thin film/NaCl) 3056 (w), 2993 (m), 1773 (s), 1262 (s), 1053 (m), 736 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.80-5.72 (m, 2H), 4.60 (dd, *J* = 1.9, 5.1 Hz, 1H), 4.42 (dd, *J* = 1.1, 5.7 Hz, 1H), 4.14 (dd, *J* = 2.2, 9.3 Hz, 1H), 2.73-2.70 (m, 1H), 1.38 (s, 6H), 1.35 (s, 3H), 0.99 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 212.3, 128.3, 125.6, 108.9, 69.6, 69.5, 63.3, 53.3, 33.8, 28.0, 26.4, 24.8, 17.0; HRMS (EI) calc'd for C<sub>13</sub>H<sub>18</sub>O<sub>3</sub> [M<sup>+</sup>] 222.1256, found 222.1255



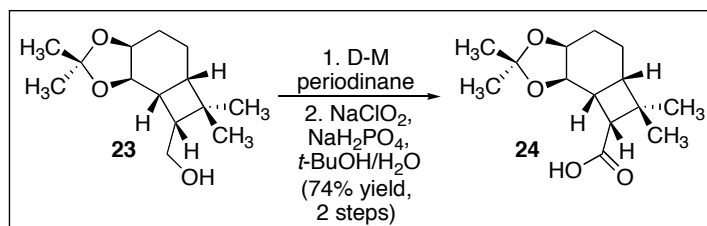
**Preparation of Ketone 21.** A solution of olefin **13** (2.00 g, 9.01 mmol, 1.0 eq.) in CH<sub>3</sub>OH (60 mL) was treated with Rh on Al<sub>2</sub>O<sub>3</sub> (10% Rh, 250 mg). The resulting suspension was purged with H<sub>2</sub> and then allowed to stir under 1 atm of H<sub>2</sub> (balloon) overnight at which point TLC indicated the complete consumption of starting material. The suspension was filtered through a small plug of celite and subsequently washed well with EtOAc. Concentration under reduced pressure was followed by purification via flash chromatography (2–5% EtOAc/hexanes eluent) to provide ketone **21** (1.43 g, 71% yield) as a white solid. m.p. 85-87 °C; FTIR (thin film/NaCl) 2937 (m), 2890 (m), 1757 (s), 1446 (w), 1376 (m), 1364 (m), 1204 (w), 1169 (m), 866 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.58 (dd, *J* = 1.9, 7.3 Hz, 1H), 4.27 (p, *J* = 3.9 Hz, 1H), 3.91 (dd, *J* = 1.5, 9.9 Hz, 1H), 2.30-2.25 (m, 1H), 2.05-1.96 (m, 1H), 1.62-1.55 (m, 1H), 1.52-1.38 (m, 2H), 1.47 (s, 3H), 1.33 (s, 6H), 1.09 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 214.2, 107.1, 71.6, 70.5, 60.0, 55.8, 32.8, 26.6, 26.2, 24.4, 24.0, 17.5, 16.6; HRMS (EI) calc'd for C<sub>13</sub>H<sub>20</sub>O<sub>3</sub> [M<sup>+</sup>] 224.1412, found 224.1411.



**Preparation of Olefin 22.** A suspension of Zn (3.39 g, 51.9 mmol, 9.0 equiv),  $\text{CH}_2\text{I}_2$  (2.10 mL, 26.1 mmol, 4.5 equiv), and a catalytic amount of  $\text{PbCl}_2$  (25 mg) in THF (45 mL) was stirred for 15 min, during which time a slightly exothermic reaction occurred. [NOTE: In the event that this slightly exothermic reaction was not observed, the reaction was heated with a heat gun for 2-3 minutes.] This suspension was cooled to 0 °C and  $\text{TiCl}_4$  (670  $\mu\text{L}$ , 6.10 mmol, 1.06 equiv) was slowly added, resulting in a very exothermic reaction. The cold bath was removed and the resulting dark brown suspension was stirred at room temperature for 30 min, at which point a solution of ketone **21** (1.29 g, 5.76 mmol, 1.0 equiv) was introduced dropwise via cannula addition over 7 min. The reaction was stirred at room temperature for 2 h before being cooled to 0 °C and carefully quenched by the addition of 1 N HCl (100 mL) (Caution!). The entire mixture was then poured into a separatory funnel containing additional 1 N HCl (250 mL) and EtOAc (100 mL). The layers are separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were then washed with 0.5 N HCl (50 mL), 50%  $\text{NaHCO}_3$  (50 mL),  $\text{H}_2\text{O}$  (50 mL), and brine. Drying over  $\text{Na}_2\text{SO}_4$  was followed by concentration *in vacuo* and purification by silica gel chromatography (2.5-3% EtOAc/hexanes eluent) to afford olefin **22** (1.09 g, 85% yield) as a pale yellow oil. FTIR (thin film/ $\text{NaCl}$ ) 2979 (m), 2950 (s), 2937 (s), 2865 (m), 1671 (w), 1447 (w), 1366 (m), 1262 (s), 1208 (m), 1046 (s), 1036 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.75 (d,  $J = 3.2$  Hz, 1H), 4.72 (d,  $J = 2.4$  Hz, 1H), 4.41 (dd,  $J = 2.1, 7.5$  Hz, 1H), 4.26 (p,  $J = 4.2$  Hz, 1H), 3.47 (dq,  $J = 2.7, 8.8$  Hz, 1H), 2.08-2.05 (m, 1H), 1.85-1.77 (m, 2H), 1.48-1.36 (m, 2H), 1.46 (s, 3H), 1.34 (s, 3H), 1.22 (s, 3H), 1.04 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) 179.0, 106.1, 74.7, 73.9, 50.7, 41.7, 39.0, 31.9, 31.7, 28.1, 26.8, 25.7, 20.1, 20.0; HRMS (FAB) calc'd for  $\text{C}_{14}\text{H}_{22}\text{O}_2$  [ $\text{M}^+$ ] 221.1542, found 221.1549.

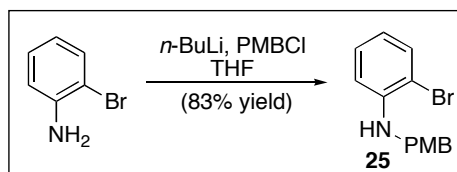


**Preparation of Alcohol 23.**  $\text{BH}_3 \cdot \text{DMS}$  (5.00 mL, 1.0 M in  $\text{CH}_2\text{Cl}_2$ , 1.13 equiv) was added dropwise over 10 min to a solution of olefin **22** (977 mg, 4.40 mmol, 1.0 equiv) in THF (15 mL) at 0 °C. The solution was allowed to slowly warm to room temperature and stir overnight. The solution was then diluted with THF (15 mL), recooled to 0 °C and treated simultaneously with 2N NaOH (3.5 mL) and 30%  $\text{H}_2\text{O}_2$  (3.5 mL). Stirring was continued at this temperature for 2 h before the reaction was quenched with 1 N HCl (25 mL), extracted with EtOAc (3 x 25 mL), washed with 5%  $\text{Na}_2\text{S}_2\text{O}_3$  (25 mL),  $\text{H}_2\text{O}$  (20 mL), and then brine. Following drying over  $\text{Na}_2\text{SO}_4$  and concentration, the derived residue was purified by flash chromatography (8-10% EtOAc/hexanes eluent) to provide alcohol **23** (660 mg, 61% yield) as a white solid. mp. 58-60 °C; FTIR (thin film/ $\text{NaCl}$ ) 3452 (b), 2940 (s), 1456 (m), 1369 (s), 1250 (s), 1216 (s), 1165 (m), 1054 (s), 868 (m), 795 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.41 (t,  $J = 7.0$  Hz, 1H), 4.26 (dt,  $J = 6.8, 9.1$  Hz, 1H), 3.81 (dd,  $J = 9.9, 11.5$  Hz, 1H), 3.67 (dd,  $J = 6.1, 11.3$  Hz, 1H), 2.47-2.36 (m, 2H), 2.21 (q,  $J = 10.2$  Hz, 1H), 2.09 (bs, 1H), 2.04-1.98 (m, 1H), 1.53-1.46 (m, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.26-1.08 (m, 2H), 1.12 (s, 3H), 0.90 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  107.9, 74.5, 73.2, 60.0, 46.0, 41.3, 37.8, 33.3, 32.2, 28.0, 26.5, 25.5, 19.6, 18.1; HRMS (EI) calc'd for  $\text{C}_{14}\text{H}_{24}\text{O}_3$  [ $\text{M}^+$ ] 240.1725, found 240.1722.



**Preparation of Acid 24.** To a solution of alcohol **23** (350 mg, 1.46 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (12 mL) at 0 °C was added pyridine (118  $\mu\text{L}$ , 1.46 mmol, 1.0 equiv) followed by Dess-Martin Periodinane (742 mg, 1.75 mmol, 1.2 equiv). The resulting suspension was allowed to stir for 2 h before being quenched by the addition of 10%  $\text{Na}_2\text{S}_2\text{O}_3$  (10 mL) and saturated  $\text{NaHCO}_3$  (20 mL).

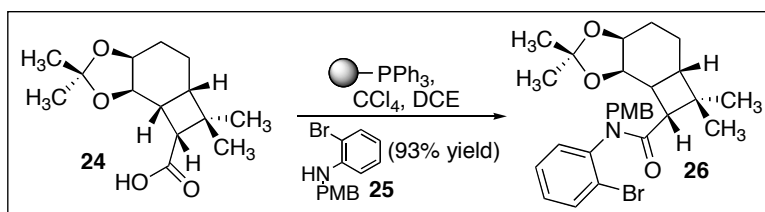
The layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers were washed with H<sub>2</sub>O (15 mL) and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to provide a residue that was filtered through a plug of silica gel (10% EtOAc/hexanes eluent) to provide an aldehyde that was carried on without further purification. To a solution of the derived aldehyde in a mixture of *t*-BuOH (19 mL) and 2,3-dimethyl-2-butene (4.5 mL) at room temperature was added a solution of NaClO<sub>2</sub> (824 mg, 9.11 mmol, 6.25 equiv) and NaH<sub>2</sub>PO<sub>4</sub> (805 mg, 5.83 mmol, 4.0 equiv) in H<sub>2</sub>O (8 mL). The colorless solution quickly became yellow and was allowed to stir at room temperature for 1 h, at which time 1 N HCl (10 mL) was added and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed successively with 5% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (25 mL), H<sub>2</sub>O (25 mL), and brine before being dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to furnish acid **24** (274 mg, 74% yield) as a white solid. Recrystallization from EtOAc/hexanes provided colorless crystals. mp. 155-156 °C; FTIR (thin film/NaCl) 2932 (b), 2903 (s), 2978 (s), 2755 (m), 1682 (s), 1451 (w), 1428 (s), 1368 (s), 1343 (m), 1234 (s), 1061 (m), 1047 (m), 879 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.42-4.35 (m, 2H), 3.06-3.00 (m, 2H), 2.12-2.05 (m, 1H), 1.87-1.82 (m, 1H), 1.63-1.50 (m, 2H), 1.45 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.20-1.10 (m, 1H), 1.03 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 179.0, 106.1, 74.7, 73.9, 50.8, 41.8, 39.0, 31.9, 31.7, 28.2, 26.8, 25.7, 20.1, 20.0; HRMS (FAB) *m/z* [calc'd for C<sub>14</sub>H<sub>23</sub>O<sub>4</sub> [M+H]<sup>+</sup> 255.1596, found 255.1595.



**Aniline 25.** To a solution of 2-bromoaniline (5.0 g, 29.1 mmol, 1.0 equiv) in THF (90 mL) at -78 °C was added *n*-BuLi (2.4 M, 12.2 mL, 1.0 equiv) over 5 min. The resulting suspension was allowed to stir for 5 min before *p*-methoxybenzyl chloride (4.0 ml, 29.5 mmol, 1.0 equiv) (PMBCl) was added dropwise over 5 min. After stirring at this temperature for 15 minutes, the bath was removed and the resulting mixture was allowed to warm to room temperature and stir overnight, at which point a brown solution remained. The reaction was quenched with 0.5 N NaOH (500 mL) and subsequently extracted with EtOAc (3 x 150 mL). The combined organic

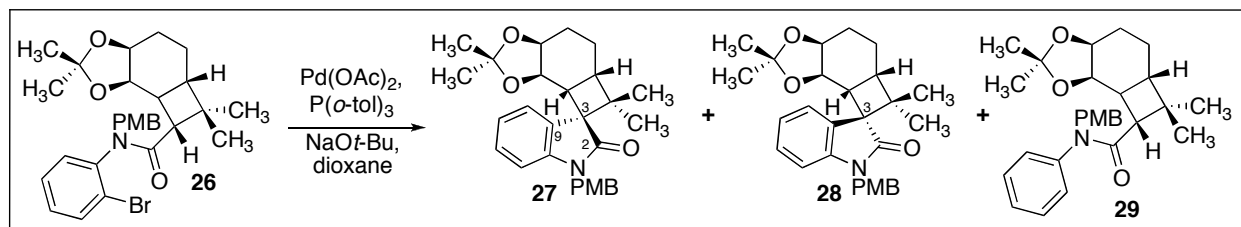


layers were washed with H<sub>2</sub>O (100 mL) then brine, dried over Na<sub>2</sub>SO<sub>4</sub> and subjected to flash chromatography (2-5% EtOAc/hexanes eluent) to provide aniline **25** (7.01 g, 83% yield) as an orange solid. An analytical sample was obtained by recrystallization from pentane/EtOAc to furnish colorless crystals. mp. 68-70 °C; FTIR (thin film/NaCl) 3399 (m), 2962 (w), 1588 (m), 1511 (m), 1425 (m), 1028 (m), 745 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.46 (dd, *J* = 1.5, 7.9 Hz, 1H), 7.32-7.30 (m, 2H), 7.16 (dt, *J* = 1.7, 7.3 Hz, 1H), 6.92-6.91 (m, 2H), 6.65 (dd, *J* = 1.0, 7.8 Hz, 1H), 6.60 (dt, *J* = 1.1, 7.2 Hz, 1H), 4.71 (bs, 1H), 4.34 (s, 2H), 3.83 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 158.9, 144.8, 132.3, 130.6, 128.5, 128.4, 117.9, 114.1, 111.6, 109.7, 55.3, 47.5; HRMS (FAB) calc'd for C<sub>14</sub>H<sub>14</sub>NOBr [M<sup>+</sup>] 291.0259, found 291.0262.



**Anilide 26.** To a suspension of aniline **25** (310 mg, 1.06 mmol, 2.0 equiv.) and acid **24** (135 mg, 0.531 mmol, 1.0 equiv.) in CCl<sub>4</sub> (1.5 mL) and dichloroethane (13.5 mL) was added polymer supported PPh<sub>3</sub> (3 mmol/g, 531 mg, 3 equiv.). The resulting suspension was heated to reflux overnight, at which point the reaction was cooled to room temperature, concentrated under reduced pressure, and filtered. Concentration and purification by flash chromatography (10-15% EtOAc/hexanes eluent) provided anilide **26** (260 mg, 93% yield), as a viscous colorless foam that existed as a mixture of rotamers. m.p 38-41 °C; FTIR (thin film/NaCl) 2981 (s), 2934 (s), 1658 (s), 1612 (m), 1584 (w), 1474 (s), 1441 (s), 1401 (s), 1244 (s), 1214 (s), 1046 (s), 880 (m), 730 (m), 604 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub> (for major rotamer) δ 7.65 (dd, *J* = 1.5, 7.2 Hz, 1H), 7.18-7.10 (m, 2H), 7.06 (app d, *J* = 8.8 Hz, 2H), 6.75 (app. d, *J* = 8.7 Hz, 2H), 6.54 (dd, *J* = 2.0, 7.4 Hz, 1H), 5.68 (d, *J* = 14.2 Hz, 1H), 4.63 (p, *J* = 5.3 Hz, 1H), 4.28 (d, *J* = 5.4 Hz, 1H), 3.81 (d, *J* = 14.1 Hz, 1H), 3.70 (s, 3H), 2.91 (t, *J* = 9.6 Hz, 1H), 2.62 (dd, *J* = 1.5, 10.2 Hz, 1H), 2.08-1.86 (m, 4H), 1.54-1.49 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 0.95 (s, 3H), 0.87 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.1, 171.6, 158.9, 158.8, 140.7, 133.6, 133.5, 131.8, 131.7, 130.5, 130.4, 129.5, 129.5, 129.4, 129.3, 128.0, 127.7, 123.9, 123.3, 113.6, 113.5, 105.9, 15.4, 74.9,

74.8, 74.5, 74.4, 55.1, 50.2, 50.1, 48.6, 42.0, 41.7.



**Oxindoles 27 and 28.** To a flask charged with *t*-BnClPd(PPh<sub>3</sub>)<sub>2</sub> (13 mg, 0.017 mmol, 0.3 equiv.), (*o*-tol)<sub>3</sub>P (5.2 mg, 0.017 mmol, 0.3 equiv.), *t*-BuONa (8.2 mg, 0.085 mmol, 1.5 equiv.), and anilide **26** (30 mg, 0.056 mmol, 1.0 equiv.) at room temperature was added dioxane (3.8 mL). The yellow/green mixture was refluxed for 4 hours during which period it turned into a slightly cloudy yellow mixture. The reaction was cooled to room temperature and quenched with saturated NH<sub>4</sub>Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H<sub>2</sub>O (10 mL) then brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration and purification of the residue by preparative TLC (15% EtOAc/hexanes eluent x 4) provided three products.

**Oxindole 27:** The least polar compound isolated was oxindole **27** (1.0 mg, 4% yield) as a colorless oil. FTIR (thin film/NaCl) 2984 (s), 2941 (s), 2870 (m), 1703 (s), 1611 (s), 1513 (s), 1486 (m), 1465 (s), 1358 (m), 1243 (m), 1179 (s), 1050 (m), 748 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.46 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.03 (dt, *J* = 1.1, 7.5 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 7.6 Hz, 1H), 5.15 (d, *J* = 15.5 Hz, 1H), 4.53 (d, *J* = 15.8 Hz, 1H), 4.32-4.30 (m, 2H), 3.77 (s, 3H), 3.26 (dd, *J* = 6.7, 10.7 Hz, 1H), 2.77-2.71 (m, 1H), 2.09-2.05 (m, 1H), 1.81-1.75 (m, 1H), 1.48 (dq, *J* = 2.1, 14.4 Hz, 1H), 1.39 (s, 3H), 1.36-1.26 (m, 1H), 1.29 (s, 3H), 1.22 (s, 3H), 0.97 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 178.5, 158.9, 143.9, 128.3, 127.8, 127.1, 125.8, 121.4, 114.1, 109.0, 107.0, 74.7, 73.2, 56.5, 55.2, 43.9, 43.2, 40.4, 39.4, 27.9, 27.1, 27.1, 26.9, 25.3, 22.6, 19.3; HRMS (EI) calc'd for C<sub>28</sub>H<sub>33</sub>NO<sub>4</sub> [M+H]<sup>+</sup> 447.2410, found 447.2411.

**Oxindole 28:** The second compound to elute was oxindole **28** (20 mg, 79% yield) as a colorless

oil. FTIR (thin film/NaCl) 2981 (s), 2932 (s), 2866 (m), 1699 (s), 1611 (s), 1513 (s), 1465 (s), 1249 (s), 1218 (m), 1173 (m), 1052 (s), 878 (m), 746 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (dd,  $J = 1.1, 7.6$  Hz, 1H), 7.21 (d,  $J = 8.9$  Hz, 2H), 7.18 (dt,  $J = 1.0, 7.3$  Hz, 1H), 7.03 (dt,  $J = 1.0, 7.5$  Hz, 1H), 6.84 (d,  $J = 9.0$  Hz, 2H), 6.72 (d,  $J = 7.6$  Hz, 1H), 5.01 (d,  $J = 15.6$  Hz, 1H), 4.61 (d,  $J = 15.6$  Hz, 1H), 4.47 (p,  $J = 5.3$  Hz, 1H), 3.82 (d,  $J = 5.5$  Hz, 1H), 3.77 (s, 3H), 3.34 (d,  $J = 9.6$  Hz, 1H), 2.46 (q,  $J = 13.8$  Hz, 1H), 2.18 (ddd,  $J = 7.7, 10.0, 12.3$  Hz, 1H), 1.95-1.90 (m, 1H), 1.70-1.64 (m, 1H), 1.43 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H), 1.16 (q,  $J = 12.3$  Hz, 1H), 1.02 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  177.9, 159.0, 143.1, 129.3, 128.6, 128.3, 128.0, 125.5, 121.8, 114.1, 108.4, 105.6, 75.1, 74.3, 58.8, 55.2, 43.0, 42.4, 40.6, 38.4, 29.3, 28.3, 27.4, 26.0, 19.9, 19.8; HRMS (EI) calc'd for  $\text{C}_{28}\text{H}_{33}\text{NO}_4$   $[\text{M}+\text{H}]^+$  447.2410, found 447.2411.

**Anilide 29:** The last compound to elute was anilide **29** (1.3 mg, 5% yield), also as a colorless oil. FTIR (thin film/NaCl) 2981 (s), 2954 (s), 2933 (s), 1649 (s), 1594 (s), 1512 (s), 1494 (s), 1403 (s), 1386 (s), 1244 (s), 1214 (s), 1165 (m), 860 (m), 701 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32-7.27 (m, 3H), 7.09 (d,  $J = 8.4$  Hz, 2H), 6.85 (d,  $J = 6.3$  Hz, 2H), 6.77 (d,  $J = 6.8$  Hz, 2H), 4.95 (d,  $J = 13.7$  Hz, 1H), 4.70 (d,  $J = 14.4$  Hz, 1H), 4.62 (p,  $J = 3.7$  Hz, 1H), 4.21 (d,  $J = 5.5$  Hz, 1H), 3.77 (s, 3H), 2.89-2.83 (m, 3H), 2.05-1.88 (m, 3H), 1.56-1.51 (s, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.9, 158.8, 142.4, 130.2, 129.9, 129.3, 128.8, 127.8, 113.6, 105.6, 75.1, 74.8, 55.1, 74.8, 55.1, 52.1, 49.7, 42.1, 38.0, 32.5, 31.1, 28.4, 27.4, 26.0, 20.2, 20.1; HRMS (EI) calc'd for  $\text{C}_{28}\text{H}_{35}\text{NO}_4$   $[\text{M}^+]$  449.2562, found 449.2564.

Screening described in Table S1 (see below) followed the above procedure, varying only the ligand and palladium source.

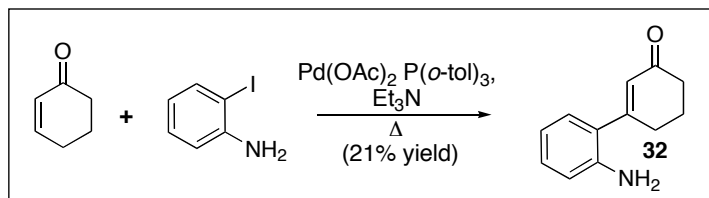
**Table S1.** Catalyst screening.<sup>a</sup>

entry	Pd source (mol %)	Ligand (mol %)	Time (h)	Conv. (%)	27 (%) <sup>b</sup>	28 (%) <sup>b</sup>	29 (%) <sup>b</sup>
1	$\text{Pd}_2(\text{dba})_3$ (30)	BINAP (45)	7	88	4	25	9
2	$\text{Pd}_2(\text{dba})_3$ (40)	BINAP (30)	6	100	16	18	0

3	Pd <sub>2</sub> (dba) <sub>3</sub> (70)	BINAP (100)	5	100	2	26	10
4	Pd(OAc) <sub>2</sub>	PCy <sub>3</sub>	6	32	0	0	6
5	Pd(OAc) <sub>2</sub>	PCy <sub>3</sub>	20	60	0	0	22
6	<i>trans</i> -BnClPd(PPh <sub>3</sub> ) <sub>2</sub> (40)	BINAP (40)	5	100	6	59	5
7	<i>trans</i> -BnClPd(PPh <sub>3</sub> ) <sub>2</sub> (40)	dppe (40)	5	100	3	59	5
8	<i>trans</i> -BnClPd(PPh <sub>3</sub> ) <sub>2</sub> (20)	dppe (20)	3	100	2	54	7
9	<i>trans</i> -BnClPd(PPh <sub>3</sub> ) <sub>2</sub> (30)	( <i>o</i> -tol) <sub>3</sub> P (30)	4	100	4	79	5
10	<i>trans</i> -BnClPd(PPh <sub>3</sub> ) <sub>2</sub> (30)	---	5	100	8	77	8
11	Pd(PPh <sub>3</sub> ) <sub>4</sub> (30)	---	7	100	10	65	8

<sup>a</sup>Conditions: Reactions carried out with 1.5 equiv. *t*-BuONa in refluxing dioxane [0.01M]. <sup>b</sup>Isolated yield.

### Preparation of 3-(2-aminophenyl)-cyclohex-2-en-1-one (32).

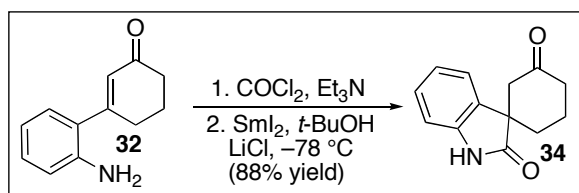


To a mixture of 2-iodoaniline (5.5 g, 25 mmol), tri-*o*-tolyl phosphine (0.75 g, 2.5 mmol) and Pd(OAc)<sub>2</sub> (0.28 g, 1.25 mmol) under an N<sub>2</sub> atmosphere was added CH<sub>3</sub>CN (150 mL), cyclohex-2-en-1-one (2.65 mL, 27.5 mmol) and Et<sub>3</sub>N (7.0 mL, 50 mmol). After stirring 24 h at reflux, the solution was cooled to rt, diluted with EtOAc (300 mL) and extracted with water (2 x 100 mL) and brine (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and purified by silica gel chromatography (gradient elution, 1% Et<sub>3</sub>N/2.5% Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>→1% Et<sub>3</sub>N/10% Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>) to give **124** as a green oil that solidified on standing at -20 °C (0.99 g, 21% yield). FTIR (KBr pellet) 3425 (s), 3340 (s), 2935 (m), 1649 (s), 1629 (s), 1606 (s), 1451 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.11-2.18 (m, 2H), 2.50 (t, *J* = 6.7 Hz, 2H), 2.66 (dt, *J* = 1.5, 6.0v, 2H), 3.87 (brs, 2H), 6.25 (t, *J* = 1.5 Hz, 1H), 6.72 (dd, *J* = 0.7, 8.1 Hz, 1H), 6.77 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.06 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.11-7.16 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 23.2, 30.3, 37.4, 116.3, 118.4, 125.6, 127.8, 128.0, 129.8, 142.9, 161.3, 199.6; HRMS (ES<sup>+</sup>) calc'd for C<sub>12</sub>H<sub>14</sub>NO [M+H]<sup>+</sup> 188.1075, found 188.1073.

### General procedure for preparation of SmI<sub>2</sub> solution in THF.

In 50 mL round bottomed flask, finely ground samarium (Strem, 0.650 g, 4.32 mmol) was quickly flame-dried *in vacuo*. Once cooled, 25 mL of dry, deoxygenated THF was added while under N<sub>2</sub> followed by addition of solid diiodoethane (0.700 g, 2.48 mmol) with vigorous stirring (Note: diiodoethane should be a fluffy white solid. Brown/tan colored diiodoethane can be purified by washing an ethereal solution with aqueous saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> followed by drying over MgSO<sub>4</sub>, filtration, concentration, and drying *in vacuo*). After about 5 min of stirring at room temperature, the mixture became a dark green-blue color, and stirring was continued for 3 h at room temperature. The deep blue solution (~0.1 M in SmI<sub>2</sub>) was allowed to settle for at least 10 min prior to use.

### Preparation of oxindole 34.

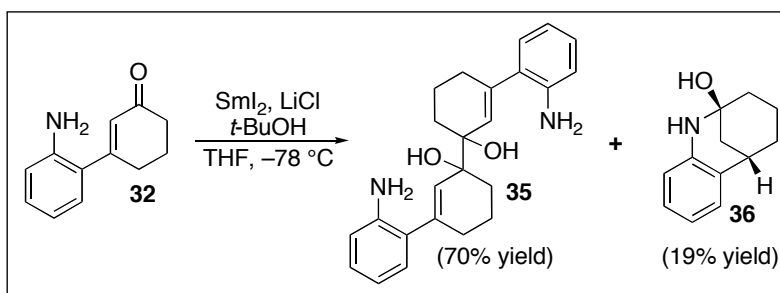


Phosgene (20% soln in toluene, 0.159 mL, 0.36 mmol) was added to a solution of enone **32** (50.0 mg, 0.27 mmol) and Et<sub>3</sub>N (0.083 mL, 0.59 mmol) in THF (1.35 mL) at 0 °C. The heterogeneous mixture was stirred at 0 °C for 30 min at which time volatile liquids were removed under reduced pressure. Dry Et<sub>2</sub>O (10 mL) was added, the resultant suspension was filtered through a pad of Celite, and the pad was washed with Et<sub>2</sub>O (10 mL). The filtrate was concentrated under reduced pressure and the residue was dissolved in dry THF (10 mL) and *t*-BuOH (0.026 mL, 0.27 mmol) was added. The solution was cooled to -78 °C and degassed by bubbling N<sub>2</sub> for 10 min. A mixture of SmI<sub>2</sub> (0.1 M soln in THF, 5.7 mL, 0.57 mmol) and LiCl (96 mg, 2.3 mmol) was stirred for 10 min at rt, then added via canula over 5 min to the isocyanate solution. After complete addition of SmI<sub>2</sub>/LiCl mixture, the reaction solution was stirred for 2 min at -78 °C, then quenched by the addition of saturated aqueous NH<sub>4</sub>Cl. The mixture was allowed to warm to room temperature, diluted with water (20 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure, and

purified by silica gel chromatography (gradient elution, 20→40% EtOAc/Hexanes). Oxindole **34** was recovered as a tan, viscous oil (51 mg, 88% yield).

**Oxindole 34.** FTIR (NaCl/thin film) 3261 (br), 1717 (s) 1618 (m), 1471 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.85-1.93 (m, 1H), 2.10-2.21 (m, 2H), 2.33-2.40 (m, 1H), 2.40 (d,  $J$  = 14.4 Hz, 1H), 2.53-2.67 (m, 2H) 2.67 (d,  $J$  = 14.4 Hz, 1H), 6.95 (d,  $J$  = 7.8 Hz, 1H), 7.04 (dt,  $J$  = 1.1, 7.7 Hz, 1H), 7.14 (d,  $J$  = 6.7 Hz, 1H), 7.24 (dt,  $J$  = 1.3, 7.7 Hz, 1H), 8.52 (brs, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.7, 32.7, 40.7, 46.2, 51.4, 110.4, 122.7, 123.7, 128.5, 132.8, 139.8, 180.8, 209.1; LRMS (ES+) calc'd for  $\text{C}_{13}\text{H}_{14}\text{NO}_2$   $[\text{M}+\text{H}]^+$  216.1025, found 216.1033. Experiments corresponding to the data presented in Table 2, entries 1-4 were performed analogously.

### Reduction of enone **32**.



A solution of enone **32** (36 mg, 0.19 mmol) and  $t\text{-BuOH}$  (18  $\mu\text{L}$ , 0.19 mmol) in THF (10 mL) was cooled to  $-78^\circ\text{C}$ , and was purged with  $\text{N}_2$  for 10 min. A mixture of  $\text{SmI}_2$  (0.1 M soln in THF, 4.0 mL, 0.40 mmol) and LiCl (67 mg, 1.6 mmol) was stirred for 10 min at rt, then added to the enone via canula over 5 min. After complete addition of the  $\text{SmI}_2/\text{LiCl}$  mixture, the reaction solution was stirred for 2 min at  $-78^\circ\text{C}$  then quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$ . The mixture was allowed to warm to rt, diluted with water (20 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, purified by silica gel chromatography (gradient elution, 1→4% MeOH/ $\text{CH}_2\text{Cl}_2$ ) to provide 7 mg (19% yield) of amina **36** as a white solid and 25 mg (70% yield) of diamino diol **35** as a 4:1 mixture of diastereomers. The diastereomers of **35** decomposed to unidentified material over the course of a few hours in solution or in a few minutes if adsorbed onto dry silica gel. They could be separated

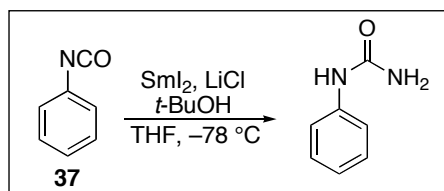
by preparative HPLC (Microsorb Si 80-120-C5, 7.5%IPA/CH<sub>2</sub>Cl<sub>2</sub>, retention time (major) = 25 min, retention time (minor) = 29 min).

**Diol 35a** [higher R<sub>f</sub> isomer (major)]: FTIR (KBr pellet) 3344 (s, br), 2936 (s), 1613 (s), 1494 (s), 1449 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 1.67 (dt, *J* = 4.0, 13.3 Hz, 1H), 1.79 (d, *J* = 13.3 Hz, 1H), 1.83-1.92 (m, 2H), 2.17-2.25 (m, 1H), 2.30 (d, *J* = 16.6 Hz, 1H), 2.67 (brs, 1H), 3.84 (brs, 1H), 5.99 (s, 1H), 6.69 (d, *J* = 8.6 Hz, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 7.0 Hz, 1H), 7.05 (dt, *J* = 1.6, 7.2 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 20.0, 30.2, 31.0, 74.5, 115.9, 118.5, 128.3, 128.5, 128.9, 129.7, 141.9, 143.9; LRMS (ES+) calc'd for C<sub>24</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 377.2229, found 377.2218.

**Diol 35b** [lower R<sub>f</sub> isomer (minor)]:, isolated in ca. 85% purity contaminated with ca. 15% of the major diastereomer. FTIR (NaCl/thin film) 3362 (m, br), 2932 (m), 1611 (m), 1493 (m), 1450 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 1.71 (dr, *J* = 4.8, 12.5 Hz, 1H), 1.82-1.91 (m, 2H), 1.95 (d, *J* = 14.1 Hz, 1H), 2.14-2.23 (m, 1H), 2.29 (d, *J* = 18.9 Hz, 1H), 2.38 (brs, 1H), 3.79 (brs, 2H), 5.91 (s, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.95 (dt, *J* = 1.0, 8.1 Hz, 1H), 7.02 (dt, *J* = 1.3, 7.7 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 19.9, 30.2, 31.1, 75.0, 116.0, 118.6, 128.4, 128.6, 128.9, 129.5, 142.8, 143.8; LRMS (ES+) calc'd for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>NaO<sub>2</sub> [M+Na]<sup>+</sup> 399.2, found 399.2.

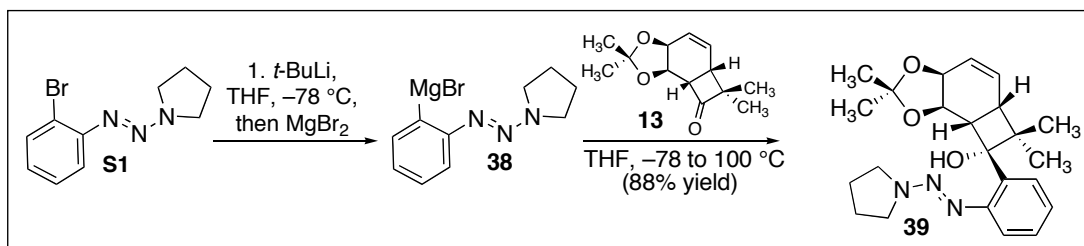
**Aminal 36**: FTIR (KBr pellet) 3507 (s), 3325 (s), 2942 (s), 2847 (m), 1606 (m), 1490 (s), 1075 (s), 1062 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.42-1.40 (m, 1H), 1.55-1.60 (m, 1H), 1.64 (t, *J* = 3.5 Hz, 1H), 1.66 (t, *J* = 3.5 Hz, 1H), 1.84 (d, *J* = 3.4 Hz, 1H), 1.87 (d, *J* = 3.4 Hz, 1H), 1.90-1.95 (m, 1H), 1.98 (d, *J* = 3.1 Hz, 1H), 2.06 (brs, 1H), 3.09-3.14 (m, 1H), 4.16 (brs, 1H), 6.50 (dd, *J* = 0.7, 7.7 Hz, 1H), 6.65 (dt, *J* = 1.6, 7.6 Hz, 1H), 7.01 (dt, *J* = 1.5, 7.7 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.5, 33.4, 36.7, 38.7, 40.7, 80.5, 113.1, 117.7, 125.6, 127.2, 128.0, 144.0; LRMS (ES+) calc'd for C<sub>12</sub>H<sub>14</sub>N [M-OH]<sup>+</sup> 172.1, found 172.2; calc'd for C<sub>12</sub>H<sub>16</sub>NO [M+H]<sup>+</sup> 190.1, found 190.2; calc'd for C<sub>12</sub>H<sub>15</sub>NNaO [M+Na]<sup>+</sup> 212.1, found 212.2.

### Reduction of Phenyl Isocyanate (37).



Freshly distilled phenyl isocyanate (0.021 mL, 0.19 mmol) was subjected to identical reaction conditions as described for enone **32** above. The reaction was quenched at  $-78\text{ }^{\circ}\text{C}$  with NaOMe (1M solution in MeOH, 1 mL) and aqueous  $\text{NH}_4\text{Cl}$  (5 mL). Following extractive workup, *N*-phenyl urea was isolated (26 mg, quant.) and found to be identical ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR) to a commercially available sample.

### Preparation of triazene **39**.



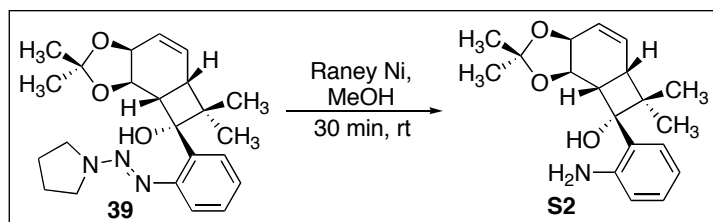
To a solution of triazene **S1**<sup>1</sup> (1.0 g, 3.94 mmol) in THF (75 mL) at  $-78\text{ }^{\circ}\text{C}$  was added *t*-BuLi (1.7M soln in pentane, 4.63 mL, 7.87 mmol). Stirring was continued at  $-78\text{ }^{\circ}\text{C}$  for 30 min, after which time a solution of  $\text{MgBr}_2$  (0.25M soln in THF, [freshly prepared from rapidly stirring 1 equiv dibromoethane and 1.2 equiv Mg turnings in THF under  $\text{N}_2$  at rt], 26.0 mL, 6.57 mmol) was added. The reaction solution was stirred at  $-78\text{ }^{\circ}\text{C}$  for 15 min, then a solution of ketone **13** (0.728 g, 3.28 mmol) in THF (15 mL) was added dropwise via canula. The reaction flask was immediately placed in a preheated oil bath ( $100\text{ }^{\circ}\text{C}$ ) and the reaction was brought to reflux. After stirring 2 min at reflux, the reaction mixture was cooled to rt, carefully quenched with water, diluted with EtOAc (200 mL) and water (100 mL). The layers were separated and the organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Analysis of the crude reaction mixture indicated that the product had been formed as a single diastereomer. Silica gel chromatography (gradient elution, 2 $\rightarrow$ 10% EtOAc/hexanes) provided 1.14 g triazene **39** (88% yield) as an orange foam.

**Triazene 39:** FTIR (KBr pellet) 3316 (m, br), 2979 (m), 2954, 2884 (m), 1418 (s), 1049 (s), 761 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.67 (s, 3H), 0.93 (s, 3H), 1.30 (s, 3H), 1.36 (s, 3H), 1.96 (brs, 4H), 2.24-2.28 (m, 1H), 3.55 (brs, 2H), 3.79 (d,  $J = 8.5\text{ Hz}$ , 1H), 3.88 (brs, 2H), 4.48 (d,  $J = 5.6\text{ Hz}$ , 1H), 4.65-4.69 (m, 1H), 5.68 (d,  $J = 10.9\text{ Hz}$ , 1H), 5.76 (ddd,  $J = 1.1, 4.2, 10.7\text{ Hz}$ , 1H), 5.88 (brs, 1H), 7.08 (dt,  $J = 1.3, 7.6\text{ Hz}$ , 1H), 7.14 (dt,  $J = 1.3, 7.6\text{ Hz}$ , 1H), 7.34 (dd,  $J = 1.1, 7.9\text{ Hz}$ , 1H), 7.38 ( $J = 1.1, 7.8\text{ Hz}$ , 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  19.2, 23.7,



23.9, 26.7, 27.5, 28.3, 24.6, 37.1, 46.1, 46.8, 51.5, 71.2, 72.0, 82.6, 107.3, 117.3, 125.2, 126.6, 127.0, 127.8, 127.9, 135.0, 148.8; HRMS (ES<sup>+</sup>) calc'd for C<sub>23</sub>H<sub>32</sub>N<sub>3</sub>O<sub>3</sub> [M+H]<sup>+</sup> 398.2444, found 398.2442]. The relative configuration was confirmed by X-ray crystallographic analysis of a more advanced intermediate (**42**, see below).

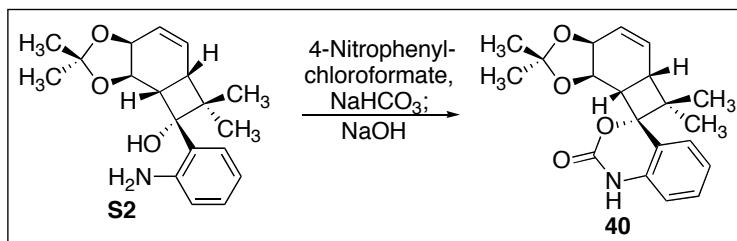
### Preparation of amino alcohol **S2**.



To a solution of triazene **39** (4.0 g, 10.0 mmol) in MeOH (1.2 L) was added a suspension of Raney Ni [400 g of 50% solution in water, prewashed with water (5x400 mL) and MeOH (3x400 mL), PYROPHORIC] in MeOH (300 mL). The reaction mixture was stirred for 30 min at rt with a mechanical stirrer. After this time, the mixture was filtered through Celite under N<sub>2</sub>, and the Celite was washed extensively with EtOAc (4L). The combined filtrates were concentrated under reduced pressure to provide the amino alcohol **S2** as a white powder. The crude amino alcohol was routinely used without purification, but chromatography on silica gel (gradient elution, 5→20% EtOAc/Hexanes) provided an analytically pure sample.

**Alcohol S2:** FTIR (NaCl/thin film): 3252 (w, br), 2983 (m), 2930 (m), 1721 (s), 1597 (m), 1370 (m), 1053 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.98 (s, 3H), 1.28 (s, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 2.35 (m, 1H), 2.38 (brs, 1H), 3.87 (dd, *J* = 1.2, 8.4 Hz, 1H), 4.12 (bs, 2H), 4.50 (d, *J* = 6.0 Hz, 1H), 4.66 (dd, *J* = 1.5, 5.6 Hz, 1H), 5.81 (ddd, *J* = 2.3, 2.3, 10.6 Hz, 1H), 5.95 (ddd, *J* = 0.6, 4.0, 10.6 Hz, 1H), 6.64 (dd, *J* = 1.0, 7.8 Hz, 1H), 6.76 (ddd, *J* = 1.2, 7.4, 7.4 Hz, 1H), 7.10 (ddd, *J* = 1.6, 7.6, 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 19.8, 26.7, 27.0, 28.3, 36.4, 37.0, 46.0, 71.0, 71.4, 83.6, 107.9, 117.2, 118.1, 126.4, 127.28, 127.31, 129.11, 129.11, 145.9; LRMS (APCI<sup>+</sup>) calc'd for C<sub>19</sub>H<sub>26</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 316.2, found 316.6.

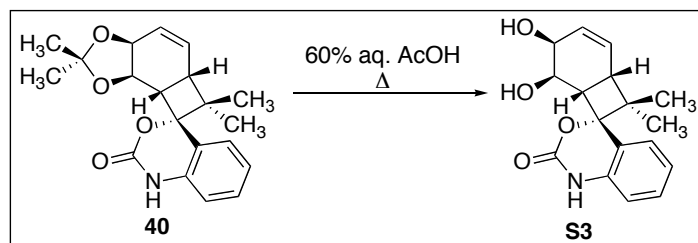
### Preparation of carbamate **40**.



To a rapidly stirring biphasic mixture of amino alcohol **S2** (~10.0 mmol), NaHCO<sub>3</sub> (1.09 g, 13 mmol), *t*-butyl methyl ether (14 mL) and water (28 mL) was added 4-nitrophenyl chloroformate (2.23 g, 11.1 mmol). The pale yellow mixture was stirred 1 h at rt at which time NaOH (23 mL of 1M solution) was added. Stirring was continued for 3 h, then the mixture was diluted with EtOAc (100 mL) and extracted with 1M NaOH (3x100 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide carbamate **40**. Crude carbamate **40** was routinely used without purification, however silica gel chromatography (gradient elution, 10→70% EtOAc/hexanes) provided an analytically pure sample.

**Carbamate 40:** FTIR (NaCl/thin film) 3453 (m), 3368 (m), 2963 (m), 1613 (m), 1453 (m), 1238 (s), 1048 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.88 (s, 3H), 1.16, (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 2.47 (m, 1H), 3.71 (d, *J* = 8.5 Hz, 1H), 4.36 (d, *J* = 6.0 Hz, 1H), 4.78 (d, *J* = 4.0 Hz, 1H), 5.76 (dd, *J* = 3.8, 10.8 Hz, 1H), 5.83 (d, *J* = 10.5 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 7.12 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.29 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 9.04 (brs, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 18.9, 26.8, 26.9, 28.3, 35.6, 37.2, 48.5, 70.1, 71.5, 90.5, 108.1, 114.8, 119.6, 123.2, 125.6, 126.2, 128.2, 129.6, 135.6, 153.7; HRMS (ES<sup>+</sup>) calc'd for C<sub>20</sub>H<sub>24</sub>NO<sub>4</sub> [M+H]<sup>+</sup> 342.1705, found 342.1696.

### Preparation of diol **S3**.

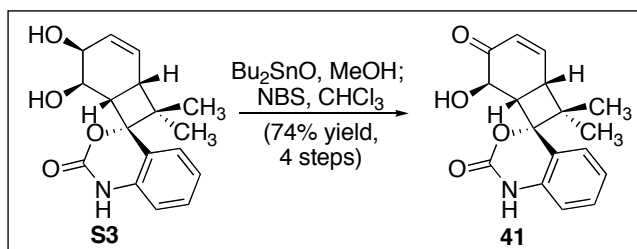


Carbamate **40** was dissolved in warm AcOH (100 mL) and water (60 mL), and the solution was stirred at 70 °C for 12 h. Upon cooling, the AcOH was quenched by adding small portions of NaOH until pH 7 was indicated by litmus paper (~64 g, 1.6 mol). The reaction

mixture was partitioned between EtOAc (400 mL total) and 1M NaOH (100 mL). The aqueous layer was extracted with EtOAc (2x100 mL). The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to provide diol **S3** as a white solid. Diol **S3** was routinely used without purification, however silica gel chromatography (gradient elution, 50% EtOAc/Hexanes→10% MeOH/EtOAc) provided an analytically pure sample.

**Diol S3:** FTIR (Nujol Mull) 3244 (w, br), 1709 (s), 1596 (m), 1068 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, MeOD-*d*<sub>3</sub>) δ 0.66 (s, 3H), 1.17 (s, 3H), 2.65 (ddd, *J* = 2.2, 3.4, 9.4 Hz, 1H), 3.36 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.25 (dd, *J* = 3.4, 5.8 Hz, 1H), 4.43 (dd, *J* = 3.2, 9.2 Hz, 1H), 5.82 (dd, *J* = 3.6 Hz, 10, 1H), 6.08, (ddd, *J* = 2.3, 5.9, 9.7 Hz, 1H) 7.95 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.17 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.30 (ddd, *J* = 1.2, 7.6, 7.6 Hz, 1H), 7.45 (d, 7.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, MeOD-*d*<sub>3</sub>) δ 21.3, 27.0, 41.1, 49.5, 42.1, 67.1, 68.1, 86.2, 115.2, 124.2, 124.5, 125.7, 129.8, 130.2, 130.6, 137.1, 154.8; HRMS (ES<sup>+</sup>) calc'd for C<sub>17</sub>H<sub>20</sub>NO<sub>4</sub> [M+H]<sup>+</sup> 302.1392, found 302.1393.

#### Preparation of α,β-unsaturated ketone **41**.

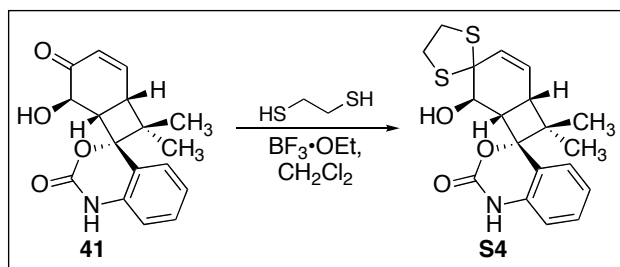


A suspension of diol **S3** (~10.0 mmol) and dibutyltin oxide (2.6g, 10.5 mmol) in MeOH (300 mL) was stirred at reflux for 3h, after which time it was cooled and concentrated under reduced pressure. To the resulting solid was added *N*-bromosuccinimide (2.05 g, 11.5 mmol) and CHCl<sub>3</sub> (100 mL). The reaction solution was stirred for 30 min at rt, diluted with 400 mL EtOAc, poured into a separatory funnel, and extracted with water (2x100 mL). The organic layer was then washed once with saturated NaHCO<sub>3</sub> and brine (50 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (gradient elution, 30→100% EtOAc/hexanes) provided α,β-unsaturated ketone **41** as a white solid (2.2g, 74% yield over 4 steps).

**Ketone 41:** FTIR (NaCl/thin film) 3408 (w, br), 2962 (s), 2963 (m), 1720 (m), 1597 (w), 1260 (s), 1092 (s), 1020 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, MeOD-*d*<sub>3</sub>) δ 0.82 (s, 3H), 1.28 (s, 3H),

2.91 (ddd,  $J = 1.0, 4.0, 9.0$  Hz, 1H), 3.35 (s, 1H), 3.52 (dd,  $J = 9.0, 7.5$  Hz, 1H), 4.76 (d,  $J = 7.0$  Hz, 1H), 6.19 (dd,  $J = 10$  Hz, 1H), 6.91 (dd,  $J = 4.0, 10.5$  Hz, 1H), 6.93 (d,  $J = 8.0$  Hz, 1H), 7.18 (dd,  $J = 7.5, 7.5$  Hz, 1H), 7.33 (dd,  $J = 7.5, 7.5$  Hz, 1H), 7.46 (d,  $J = 8.0$  Hz, 1H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{MeOD-d}_3$ )  $\delta$  20.8, 26.5, 40.8, 45.8, 51.2, 69.9, 86.4, 115.3, 122.4, 124.4, 125.6, 129.6, 130.5, 137.1, 148.1, 154.0, 199.8; HRMS (ES $^{+}$ ) calc'd for  $\text{C}_{17}\text{H}_{18}\text{NO}_4$   $[\text{M}+\text{H}]^{+}$  300.1236, found 300.1234.

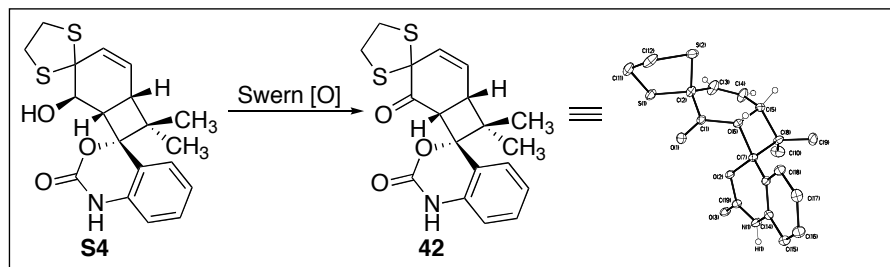
#### Preparation of dithiolane **S4**.



To a solution of  $\alpha,\beta$ -unsaturated ketone **41** (245.0 mg, 0.81 mmol) and 1,2-ethanedithiol (0.103 mL, 1.20 mmol) in  $\text{CH}_2\text{Cl}_2$  (16 mL) at  $0^\circ\text{C}$  was added  $\text{BF}_3\cdot\text{Et}_2\text{O}$  (0.123 mL, 0.97 mmol). The reaction mixture was stirred at  $0^\circ\text{C}$  for 5h, after which time saturated aqueous  $\text{NaHCO}_3$  (1 mL) was added. The mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  (50 mL) and saturated aqueous  $\text{NaHCO}_3$  (50 mL). The layers were separated and the aqueous layer was back extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL). The combined organic layers were dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (gradient elution, 10 $\rightarrow$ 20%  $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ ) provided alcohol **S4** as a white solid in approximately 95% purity; this material converted directly into ketone **42**.

**Alcohol S4:** FTIR (NaCl/thin film) 3446 (w, br), 3250 (w, br), 2925 (w), 1717 (s), 1597 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.66 (s, 3H), 1.25 (s, 3H), 2.61 (ddd,  $J = 2.6, 3.3, 9.8$  Hz, 1H), 2.66 (d,  $J = 4.9$  Hz, 1H), 3.30-3.45 (m, 4H), 3.51-3.54 (m, 1H), 4.80 (dd,  $J = 4.8, 9.8$  Hz, 1H), 5.58 (dd,  $J = 3.6, 9.4$  Hz, 1H), 6.18 (dd,  $J = 2.0, 9.6$  Hz, 1H), 6.85 (dd,  $J = 0.8, 7.9$  Hz, 1H), 7.17 (dt, 1.0, 7.7 Hz, 1H), 7.28 (dt, 1.3, 7.8 Hz, 1H), 7.39 (d, 7.6 Hz, 1H), 8.37 (brs, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.1, 26.5, 40.0, 41.1, 41.7, 44.6, 49.0, 69.2, 72.4, 84.4, 114.3, 122.5, 123.6, 124.2, 124.9, 129.2, 134.7, 135.0, 152.9; HRMS (ES $^{+}$ ) calc'd for  $\text{C}_{19}\text{H}_{22}\text{NO}_3\text{S}_2$   $[\text{M}+\text{H}]^{+}$  376.1041, found 376.1034.

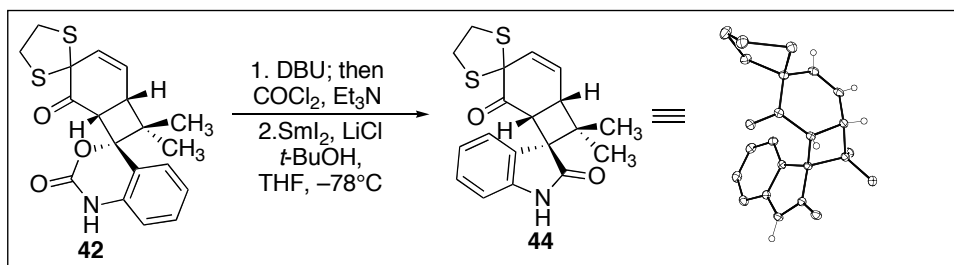
## Preparation of ketone **42**.



To a solution of  $(\text{COCl})_2$  (0.089 mL, 1.01 mmol) in  $\text{CH}_2\text{Cl}_2$  (7 mL) at  $-78^\circ\text{C}$  was added DMSO (0.142 mL, 2.02 mmol). The reaction mixture was stirred for 15 min at  $-78^\circ\text{C}$ , and then alcohol **S4** (190 mg, 0.5 mmol) was added dropwise as a solution in  $\text{CH}_2\text{Cl}_2$  (25 mL). The temperature of the dry ice/acetone bath was allowed to warm to  $-65^\circ\text{C}$  over 20 min after which time  $\text{Et}_3\text{N}$  (0.57 mL, 4.04 mmol) was added. The reaction mixture was stirred at  $-65^\circ\text{C}$  for 5 min and  $-20^\circ\text{C}$  for 20 min and then quenched with saturated aqueous  $\text{NaHCO}_3$ . The reaction mixture was partitioned between  $\text{CH}_2\text{Cl}_2$  (100 mL) and 1M  $\text{HCl}$  (100 mL). The organic layer was extracted with 1M  $\text{HCl}$  (2x100 mL) and brine (50 mL), dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Purification by silica gel chromatography (10%  $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$ ) provided ketone **42** as a tan solid (140 mg, 75% yield; 46% yield from **41**). Crystals suitable for X-ray diffraction were grown by slow evaporation from  $\text{CH}_2\text{Cl}_2$ /Hexanes. For crystallographic details, see Appendix 2.1.

**Ketone 42:** FTIR (KBr pellet) 3426 (w, br), 2929 (w), 1719 (s), 1598 (m), 1346 (m), 1061 (w), 758 (w)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.92 (s, 3H), 1.24 (s, 3H), 2.95 (ddd,  $J = 2.7, 2.7, 8.6$  Hz, 1H), 3.29 (ddd,  $J = 6.6, 8.1, 11.6$  Hz, 1H), 3.39 (ddd,  $J = 4.2, 5.6, 11.6$  Hz, 1H), 3.51-3.62 (m, 2H), 4.34 (d,  $J = 8.6$  Hz, 1H), 6.06 (dd,  $J = 2.5, 9.9$  Hz, 1H), 6.21 (dd,  $J = 2.3, 10.2$  Hz, 1H), 6.71 (dd,  $J = 0.9, 7.8$  Hz, 1H), 7.11 (dt,  $J = 1.1, 7.6$  Hz, 1H), 7.15 (brs, 1H), 7.25-7.29 (m, 1H), 7.33 (d,  $J = 7.7$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.1, 25.9, 41.0, 42.3, 43.2, 47.9, 66.4, 90.3, 91.4, 113.9, 119.2, 122.1, 126.6, 127.3, 129.4, 131.5, 135.8, 150.8, 197.9; LRMS (ES+) calc'd for  $\text{C}_{19}\text{H}_{19}\text{NNaO}_3\text{S}_2$   $[\text{M}+\text{Na}]^+$  396.1, found 396.1.

### Preparation of oxindole **44**.

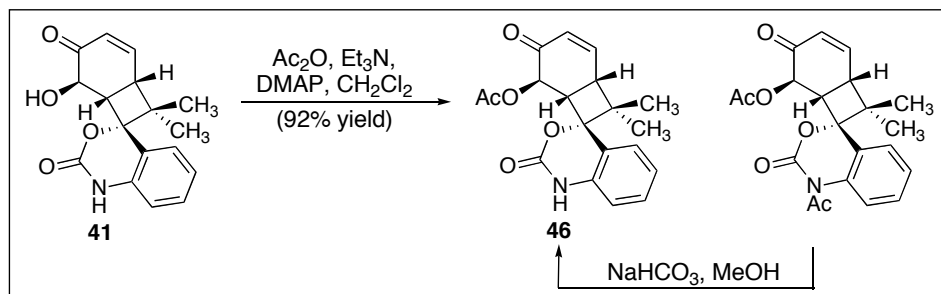


To a solution of ketone **42** (25 mg, 0.067 mmol) in THF (0.7 mL) was added 1,8-diazabicyclo[4.3.0]undec-7-ene (DBU, 0.004 mL, 0.026 mmol). After 3h, TLC analysis indicated complete consumption of the starting material. The reaction mixture was cooled to  $0^\circ\text{C}$ , and  $\text{Et}_3\text{N}$  (0.019 mL, 0.13 mmol) and phosgene (20% solution in toluene, 0.041 mL, ca. 0.084 mmol) were added. After 30 min, the reaction mixture was concentrated under reduced pressure, suspended in dry  $\text{Et}_2\text{O}$  (10 mL) and filtered through a pad of Celite. The Celite was washed with  $\text{Et}_2\text{O}$  (10 mL) and the combined filtrate was concentrated under reduced pressure. The resulting residue was dissolved in dry THF (0.6 mL) and cooled to  $-78^\circ\text{C}$ . Following addition of  $t\text{-BuOH}$  (6.4  $\mu\text{L}$ , 0.067 mmol), the reaction solution was degassed by bubbling  $\text{N}_2$  for 10 min. A mixture of  $\text{SmI}_2$  (0.1M solution in THF, 1.4 mL 0.14 mmol) and  $\text{LiCl}$  (11 mg, 0.27 mmol) that had been premixed for 10 min was added dropwise over 5 min. Stirring was maintained for 30 min at which time the reaction was quenched at  $-78^\circ\text{C}$  with saturated aqueous  $\text{NH}_4\text{Cl}$ . The mixture was allowed to warm to rt, diluted with  $\text{EtOAc}$  (30 mL) and washed with saturated aqueous  $\text{NH}_4\text{Cl}$ . The organic layer was dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Analysis of the crude reaction mixture by  $^1\text{H}$  NMR indicated the product had been formed as a 7:1 mixture of diastereomers [integration of the peaks corresponding to the proton adjacent to the carbonyl, 3.8 ppm (major), 3.6 ppm (minor)]. The desired oxindole **44** was isolated as a white solid as a 7:1 mixture of diastereomers (17 mg, 71% yield) following silica gel chromatography (gradient elution, 0.5 $\rightarrow$ 2%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ). Slow evaporation from  $\text{MeOH}$  provided a single crystal suitable for x-ray crystallographic analysis. See Appendix 2.2 for x-ray crystallographic details.

**Oxindole 44:** FTIR (KBr pellet) 3172 (w, br), 2926 (w), 1696 (s), 1608 (m), 1467 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3/\text{DMSO}-d_6$ , 2:1)  $\delta$  0.65 (s, 3H), 1.01 (s, 3H), 2.91 (ddd,  $J = 5.8, 5.8, 11.7$  Hz, 1H), 3.14 (ddd,  $J = 4.9, 4.9, 11.6$  Hz, 1H), 3.28-3.32 (m, 2H), 3.38 (ddd,  $J = 1.6, 3.8, 9.4$  Hz, 1H), 3.79 (d,  $J = 9.4$  Hz, 1H), 5.73 (dd,  $J = 4.0, 9.8$  Hz, 1H), 5.96 (dd,  $J = 1.9, 9.9$

Hz, 1H), 6.58 (d,  $J = 7.6$  Hz, 1H), 6.66 (dt, 1.0, 7.6 Hz, 1H), 6.77 (dd,  $J = 0.5$ , 7.3 Hz, 1H), 6.89 (dt,  $J = 1.3$ , 7.6 Hz, 1H), 9.56 (brs, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3/\text{DMSO}-d_6$ , 2:1)  $\delta$  22.7, 24.7, 28.9, 40.9, 42.3, 44.4, 45.1, 57.8, 66.1, 109.1, 120.2, 125.3, 127.3, 127.5, 128.0, 130.1, 142.0, 179.0, 199.1; LRMS (ES $^{+}$ ) calc'd for  $\text{C}_{19}\text{H}_{19}\text{NNaO}_2\text{S}_2$   $[\text{M}+\text{Na}]^{+}$  380.1, found 380.1.

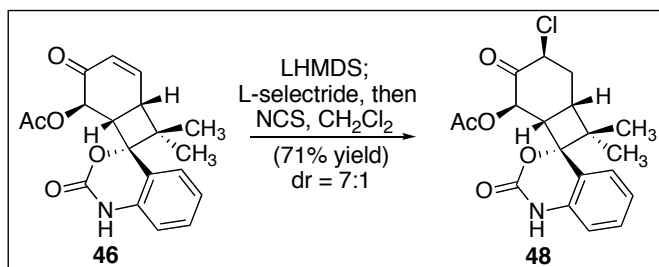
### Preparation of acetate **46**.



To a solution of enone **41** (900 mg, 3.01 mmol) in  $\text{CH}_2\text{Cl}_2$  (30 mL) was sequentially added  $\text{Et}_3\text{N}$  (0.630 mL, 4.50 mmol), DMAP (37.0 mg, 0.30 mmol), then  $\text{Ac}_2\text{O}$  (0.360 mL, 3.89 mmol) and the reaction was stirred for 1 h at room temperature. TLC showed complete conversion to two spots, assigned the mono-acetate **46** and the corresponding di-acetate. The reaction was partitioned between  $\text{CH}_2\text{Cl}_2$  and 0.1 M HCl, and the organic layer was dried over  $\text{MgSO}_4$ . Filtration followed by concentration under reduced pressure and purification by silica gel chromatography (gradient elution, 30%  $\rightarrow$  60% EtOAc/Hexanes) provided 841 mg acetate **46** and 162 mg of di-acetate. The diacetate was treated with  $\text{NaHCO}_3$  (100 mg, 1.35 mmol) in MeOH (10 mL) for 2 h. Concentration of the reaction mixture and purification by silica gel chromatography (gradient elution, 30% $\rightarrow$ 60% EtOAc/Hexanes) provided an additional 105 mg **46** (946 mg total, 92% yield) as a white powder.

**Acetate 46:** FTIR (NaCl/thin film) 2961 (s), 2920 (s), 2850 (s), 1734 (s), 1463 (m), 1261 (s), 1074 (s), 1022 (s), 865 (s), 801 (s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65 (brs, 1H), 7.31 (dt,  $J = 7.6$ , 1.2 Hz, 1H), 7.26 (d, overlapping  $\text{CDCl}_3$ , 1H), 6.82 (m, 2H), 6.29 (dd,  $J = 10.0$ , 2.0 Hz, 1H), 5.80 (d,  $J = 7.2$  Hz, 1H), 3.68 (dd,  $J = 9.2$ , 7.2 Hz, 1H), 2.85 (ddd,  $J = 9.2$ , 4.0, 2.0 Hz, 1H), 2.11 (s, 3H), 1.56 (s, 3H), 1.35 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  192.3, 169.8, 152.7, 146.0, 135.4, 129.9, 129.6, 124.1, 123.6, 120.2, 115.0, 85.6, 70.2, 50.5, 41.5, 39.8, 26.4, 21.0, 20.5; HRMS (ES $^{+}$ ) calc'd for  $\text{C}_{19}\text{H}_{20}\text{NO}_5$   $[\text{M}+\text{H}]^{+}$  342.1341, found 342.1341.

### Preparation of chloro-ketone **48**.

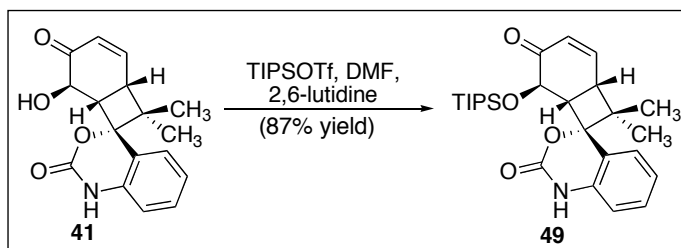


To a solution of acetate **46** (500.0 mg, 1.47 mmol) in THF (37 mL) cooled to  $-78^{\circ}\text{C}$  under  $\text{N}_2$  and was added LHMDS (1M solution in THF, 1.60 mL, 1.60 mmol). The reaction was stirred 15 min, then L-selectride (1M solution in THF, 1.60 mL, 1.60 mmol) was added and the reaction was stirred an additional 30 min. After this time, a solution of NCS (0.49 M solution prepared by dissolving 1.38 g (10.3 mmol) NCS in 21.0 mL THF) was added via canula and the reaction was stirred 30 min longer then quenched at  $-78^{\circ}\text{C}$  by addition of saturated aqueous  $\text{NaHCO}_3$  and diluted with EtOAc. The aqueous layer was partitioned with EtOAc (200 mL total), the combined organic extracts were washed with water (2 x 30 mL), brine, and dried over  $\text{MgSO}_4$ . Filtration followed by concentration under reduced pressure and purification by silica gel chromatography (gradient elution, 30%  $\rightarrow$  60% EtOAc/Hexanes) to give 397 mg (71% yield) of chloro-ketone **48** as a 7:1 mixture of diastereomers.

**Chloro-Ketone 48:** FTIR (NaCl/thin film) 3243 (m, br), 2964 (m), 1734 (s), 1597 (m), 1373 (m), 1230 (s), 1061 (s), 915 (m), 732 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.76 (s, 1H), 7.31 (t,  $J = 8.0$  Hz, 1H), 7.21 (d,  $J = 7.5$  Hz, 1H), 7.13 (t,  $J = 7.5$  Hz, 1H), 6.89 (d,  $J = 8.0$  Hz, 1H), 6.08 (d,  $J = 9.0$  Hz, 1H), 4.73 (d,  $J = 4.5$  Hz, 1H), 3.58 (t,  $J = 9.0$  Hz, 1H), 3.22 (ddd,  $J = 14.5, 14.5, 5.0$  Hz, 1H), 2.48 (ddd,  $J = 13.0, 9.5, 4.5$  Hz, 1H), 2.30 (dd,  $J = 14.5, 4.5$  Hz, 1H), 2.03 (s, 3H), 1.28 (s, 3H), 0.88 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  199.5, 169.7, 152.8, 135.0, 129.8, 125.4, 123.5, 119.5, 114.7, 88.6, 71.1, 58.2, 47.2, 38.8, 35.6, 32.1, 27.0, 20.7, 18.8; HRMS (ES<sup>+</sup>) calc'd  $\text{C}_{19}\text{H}_{21}\text{NO}_5\text{Cl}$   $[\text{M}+\text{H}]^+$  378.1108, 378.1106.



### Preparation of TIPS ether **49**.



To a solution of enone **41** (2.50 g, 8.40 mmol) dissolved in 42 mL DMF was added 2,6-lutidine (5.87 mL, 50.0 mmol). The solution was cooled to 0 °C while stirring under N<sub>2</sub> and TIPSOTf (6.77 mL, 25.0 mmol) was added over 5 min. The reaction mixture was warmed to room temperature and stirred for 1½ h, then quenched by addition of 100 mL saturated aqueous NaHCO<sub>3</sub> and diluted with Et<sub>2</sub>O. The aqueous layer was partitioned with Et<sub>2</sub>O (500 mL total) and combined ethereal extracts were washed once with brine, then dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure, and the crude material was purified by silica gel chromatography (gradient elution, 10→50% EtOAc/Hexanes) to give 3.30 g (87% yield) of **49** as a white solid.

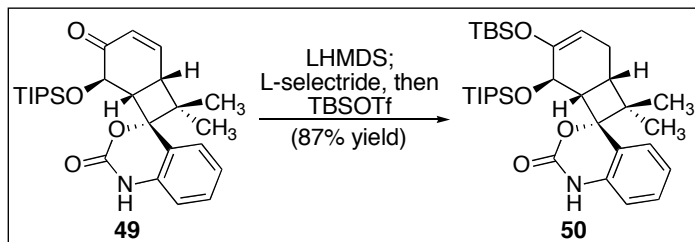
**TIPS Ether 49:** FTIR (NaCl/thin film): 3264 (m, br), 3104 (w), 2943 (s), 2866 (s), 1725 (s), 1598 (m), 1489 (m), 1463 (m), 1352 (m), 1248 (m), 1096 (m), 1068 (s), 882 (m), 753 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.33 (brs, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.82 (dd, *J* = 10.0, 4.0 Hz, 1H), 6.28 (dd, *J* = 10.0, 1.5, 1H), 4.52 (d, *J* = 4.0 Hz, 1H), 3.67 (dd, *J* = 8.5, 4.5 Hz, 1H), 2.76 (ddd, *J* = 8.5, 4.0, 1.5 Hz, 1H), 1.24 (s, 3H), 1.15 (septet, *J* = 7.5 Hz, 3H), 1.02 (m, 18H), 0.91 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 194.7, 153.0, 146.2, 135.1, 129.7, 129.1, 124.6, 123.2, 119.5, 115.0, 88.5, 69.5, 50.1, 43.6, 39.4, 26.7, 19.8, 18.1, 18.1, 12.5; HRMS (ES<sup>+</sup>) calc'd for C<sub>26</sub>H<sub>38</sub>NO<sub>4</sub>Si [M+H]<sup>+</sup> 456.2570, found 456.2570.

Note: use of old TIPSOTf resulted in epimerization at C11 (~4:1 to 9:1 β to α).

**TIPS Ether 11-*epi*-49:** FTIR (NaCl/thin film) 3263 (m, br), 2957 (m), 2866 (m), 1724 (s), 1598 (m), 1352 (m), 1068 (m), 733 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.56 (brs, 1H), 7.28 (m, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.79 (dd, *J* = 10.4, 4.8 Hz, 1H), 6.25 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.52 (d, *J* = 4.4 Hz, 1H), 3.61 (dd, *J* = 8.8, 4.4 Hz, 1H), 2.76 (ddd, *J* = 8.8, 4.4, 1.6 Hz, 1H), 1.33 (m, 1H), 1.24 (s, 3H), 0.96 (m, 18H), 0.68 (m, 2H); <sup>13</sup>C

NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  195.2, 152.4, 145.9, 135.4, 129.7, 129.2, 124.7, 123.3, 119.9, 114.7, 88.0, 69.5, 50.0, 44.0, 39.5, 26.7, 20.0, 18.8, 17.9, 17.8, 17.74, 17.73, 17.2, 13.9, 13.2, 12.95, 12.85; HRMS (ES<sup>+</sup>) calc'd for C<sub>26</sub>H<sub>38</sub>NO<sub>4</sub>Si [M+H]<sup>+</sup> 456.2570, found 456.2580.

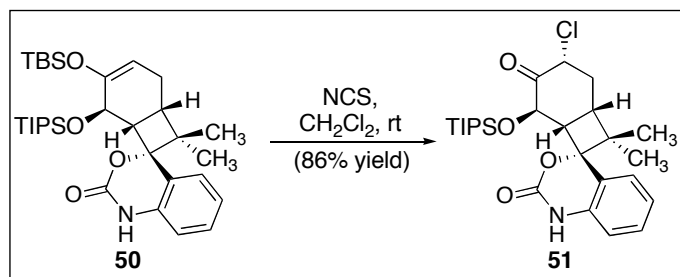
### Preparation of silyl enol ether **50**.



To a solution of TIPS ether **49** (54.0 mg, 0.118 mmol) in THF (5 mL) was added LHMDS (1.0 M in THF, 0.166 mL, 0.166 mmol) while stirring under N<sub>2</sub> at –78 °C. After stirring 15 min at this temperature, L-selectride® (1.0 M in THF, 0.199 mL, 0.199 mmol) was added and reaction was stirred 45 min before addition of TBSOTf (80  $\mu$ L, 0.354 mmol). The reaction was stirred an additional 30 min at –78 °C and was then quenched with saturated NaHCO<sub>3</sub> and diluted with EtOAc. The aqueous layer was partitioned with EtOAc (150 mL total) and the combined organic extracts were washed once with brine and dried over MgSO<sub>4</sub>. Upon filtration, the solvent was removed under reduced pressure and the crude residue was purified by silica gel chromatography (gradient elution, 0  $\rightarrow$  20% EtOAc/Hexanes) to give 59 mg (87% yield) of **50** as a white foam.

**Silyl Enol Ether 50:** FTIR (NaCl/thin film) 3238 (w, br), 3104 (w), 2928 (s), 2864 (s), 1722 (s), 1598 (m), 1348 (m), 1259 (m), 1202 (m), 1061 (m), 887 (m), 839 (m), 750 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.18 (s, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.22 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.09 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.81 (dd, *J* = 7.5, 0.5 Hz, 1H), 4.89 (dd, *J* = 7.0, 2.0 Hz, 1H), 3.59 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.45 (ddd, *J* = 16.5, 7.5, 3.0 Hz, 1H), 2.21 (dd, *J* = 8.0, 8.0 Hz, 1H), 2.13 (dd, *J* = 16.5, 7.5 Hz, 1H) 1.22 (s, 3H), 1.10 (m, 3H), 1.03 (m, 18 H), 0.99 (s, 9H), 0.63 (s, 3H), 0.40 (s, 3H), 0.30 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  153.9, 153.5, 135.8, 128.8, 125.1, 122.7, 122.2, 114.1, 101.7, 87.7, 67.9, 46.4, 45.9, 36.3, 28.3, 26.1, 25.8, 21.6, 18.9, 18.40, 18.39, 18.3, 12.8, -4.1, -4.3; LRMS (ES<sup>+</sup>) calc'd for C<sub>32</sub>H<sub>53</sub>NO<sub>4</sub>Si<sub>2</sub> [M+H]<sup>+</sup> 472.3, found 472.4.

### Preparation of chloro-ketone **51**.

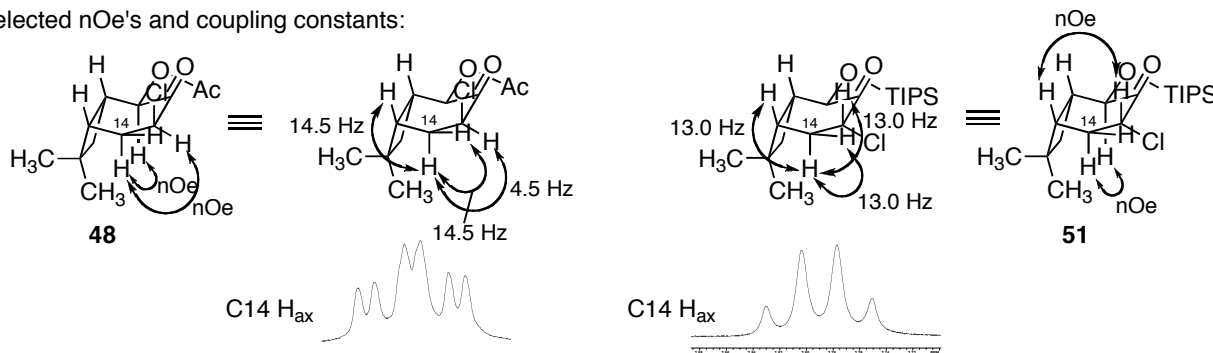


To a solution of silyl enol ether **50** (73 mg, 0.128 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) stirring at room temperature was sequentially added acetic anhydride (40.0  $\mu$ L, 0.383 mmol) and NCS (51.0 mg, 0.383 mmol). The resulting solution was stirred 5 minutes then quenched by addition of silica gel. The reaction mixture was concentrated onto silica gel and purified by silica gel chromatography (gradient elution, 10  $\rightarrow$  30% EtOAc/Hexanes) to give 63 mg (86% yield) of **51** as a white foam.

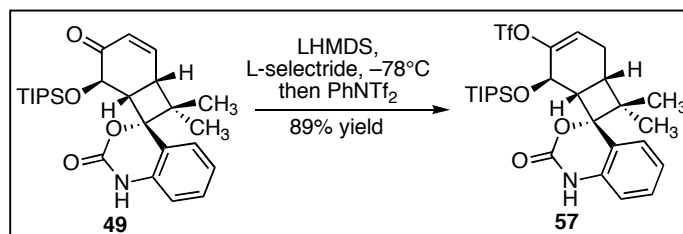
**Chloro-Ketone 51:** FTIR (NaCl/thin film) 3253 (m, br), 3107 (w), 2945 (s), 2867 (s), 2252 (w), 1724 (s), 1598 (m), 1463 (m), 1352 (m), 1252 (m), 1156 (m), 1059 (m), 734 (m), 682 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.76 (brs, 1H), 7.26 (m, 1H), 7.22 (d,  $J$  = 7.5 Hz, 1H), 7.07 (t,  $J$  = 7.5 Hz, 1H), 6.87 (d,  $J$  = 7.0 Hz, 1H), 5.43 (d,  $J$  = 7.5 Hz, 1H), 4.16 (dd,  $J$  = 12.5, 6.0 Hz, 1H), 3.40 (dd,  $J$  = 8.0, 8.0 Hz, 1H), 2.88 (ddd,  $J$  = 13.0, 13.0, 13.0 Hz, 1H), 2.41 (m, 1H), 2.04 (m, 1H), 1.24 (s, 3H), 1.84 (m, 24H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  204.8, 171.2, 134.9, 129.7, 126.2, 123.3, 119.5, 114.5, 90.0, 70.4, 55.3, 47.6, 43.2, 38.2, 33.2, 28.1, 27.1, 18.5, 17.8, 17.6, 12.2; HRMS (ES<sup>+</sup>) calc'd for C<sub>26</sub>H<sub>39</sub>NO<sub>4</sub>ClSi [M+H]<sup>+</sup> 492.2337, found 492.2324.

Comparison of the <sup>1</sup>H NMR spectra of  $\alpha$ -chloroketones **48** and **51** revealed distinct splitting patterns for the C14<sub>ax</sub> proton depending on whether the C13 chlorine was “up” or “down.” The C14<sub>ax</sub> coupling constants for **48** were characteristic of one geminal, one axial and one equatorial proton coupling, while the C14<sub>ax</sub> coupling constants for **51** were characteristic of one geminal and two axial proton couplings [carbamate was omitted from drawing for clarity].

selected nOe's and coupling constants:



### Preparation of enol triflate **57**.

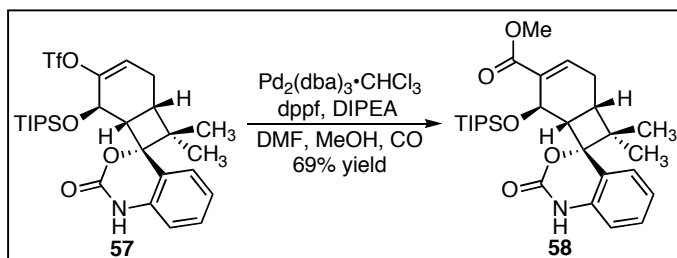


To a solution of enone **49** (6.00 g, 13.2 mmol) in THF (50 mL) cooled to -78 °C was added LHMDS (1.0 M solution in THF, 14.50 mL, 14.50 mmol) and the reaction was stirred under N<sub>2</sub> for 20 min before addition of L-selectride (1.0 M solution in THF, 15.84 mL, 15.84 mmol). After stirring 2 h with slow warming from -78 °C to -60 °C, a solution of Tf<sub>2</sub>NPh (9.42 g, 26.40 mmol) in 20 mL of THF was added via cannula and the reaction mixture was gradually warmed to room temperature and stirred for an additional 4 h. The reaction was quenched by addition of saturated aqueous NaHCO<sub>3</sub> and the aqueous layer was partitioned with a total of 600 mL EtOAc. The combined EtOAc extracts were washed once with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude residue was purified silica gel chromatography (gradient elution, 5 → 40% EtOAc/Hexanes) to give 6.70 g (89% yield) of **57** as a white solid.

**Enol Triflate 57:** FTIR (NaCl/thin film) 3260 (m, br), 3103 (w), 2945 (s), 2868 (s), 2253 (w), 1725 (s), 1598 (m), 1420 (m), 1350 (m), 1210 (s), 1144 (s), 1066 (m), 884 (m), 754 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.39 (s, 1H), 7.27 (m, 2H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.01 (t, *J* = 4.5 Hz, 1H), 4.85 (s, 1H), 3.59 (dd, *J* = 10.0, 2.5 Hz, 1H), 2.54 (ddd, *J* = 18.0, 8.5, 4.5 Hz, 1H), 2.46 (m, 1H), 2.31 (ddd, *J* = 10.0, 8.5, 4.5 Hz, 1H), 1.87 (s, 3H), 1.06 (m, 3H), 1.03 (m, 18H), 0.74 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 153.3, 150.2, 135.4,

129.5, 124.9, 123.0, 120.4, 118.2, 114.8, 88.1, 66.8, 47.3, 47.0, 35.20, 27.1, 22.3, 18.4, 18.2, 12.8. HRMS (ES<sup>+</sup>) calc'd for C<sub>27</sub>H<sub>39</sub>NO<sub>6</sub>SiF<sub>3</sub>S [M+H]<sup>+</sup> 590.2219, found 590.2222.

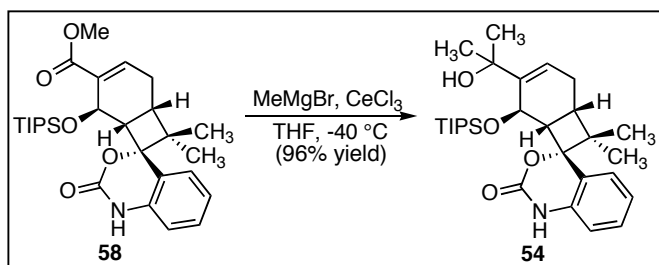
### Preparation of ester **58**.



In a 500 mL flask, powdered molecular sieves (1.0 g) were flame-dried *in vacuo*. After cooling to room temperature, vinyl triflate **57** (6.70 g, 11.30 mmol) was added followed by DMF (40 mL) and MeOH (10 mL, 247 mmol). The resulting mixture was stirred vigorously under N<sub>2</sub> for 30 min, after which time DIPEA (7.88 mL, 45.2 mmol), dppf (537 mg, 0.966 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (500 mg, 0.483 mmol) were added sequentially. The flask was fitted with a reflux condenser and the orange mixture was purged with CO for 5 min, then heated to 60 °C under a CO atmosphere for 1½ h. The reaction was cooled to room temperature, diluted with Et<sub>2</sub>O (100 mL) and filtered through Celite. The sieves were washed several times with Et<sub>2</sub>O, and the filtrate was washed with 150 mL of water. The aqueous layer was back-extracted with several portions of Et<sub>2</sub>O (500 mL total) and the ethereal extracts were washed once with brine and dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure, and the crude brown residue was purified by silica gel chromatography (gradient elution, 0→30% EtOAc/Hexanes) to give 3.90 g (69% yield) of **58** as a white powder.

**Ester 58:** FTIR (NaCl/thin film): 3269 (m, br), 2944 (s), 2865 (s), 1722 (s), 1597 (m), 1348 (m), 1255 (s), 1060 (s), 915 (w), 882 (m), 737 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.84 (s, 1H), 7.28 (m, 3H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.11 (d, *J* = 2.0 Hz, 1H), 3.79 (s, 3H) 3.68 (dd, *J* = 9.6, 2.0 Hz, 1H), 2.54 (ddd, *J* = 18.0, 8.4, 2.8 Hz, 1H), 2.36 (m, 2H), 1.05 (m, 24H), 0.66 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 153.3, 141.3, 135.5, 135.5, 129.1, 125.0, 122.8, 121.5, 114.4, 87.5, 51.7, 46.1, 44.2, 36.6, 28.1, 23.2, 19.2, 18.3, 18.2, 12.6; HRMS (ES<sup>+</sup>) calc'd for C<sub>28</sub>H<sub>42</sub>NO<sub>5</sub>Si [M+H]<sup>+</sup> 500.2832, found 500.2853.

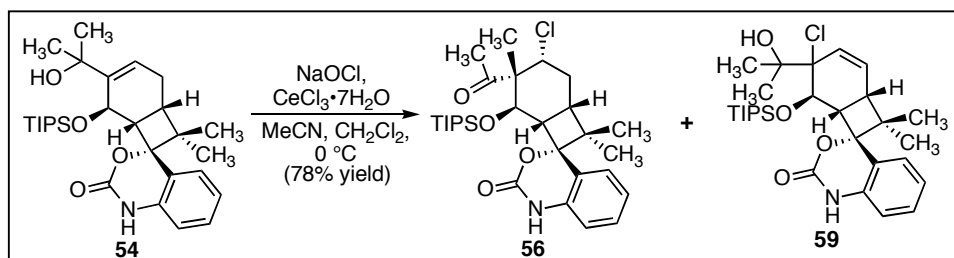
### Preparation of alcohol **54**.



In a 500 mL flask fitted with a CaCl<sub>2</sub> drying tube, CeCl<sub>3</sub>·7H<sub>2</sub>O (17.40 g, 46.80 mmol) was heated to 120 °C *in vacuo* for 12 h, then cooled to room temperature under N<sub>2</sub>. The flask was quickly fitted with a septum, 50 mL of THF was added, and the resulting slurry was stirred vigorously for 1 hour at room temperature. A solution of ester **58** (3.90 g, 7.80 mmol) in 15 mL THF was added via cannula (rinsed with 5 mL THF) and the mixture was stirred for 30 min at room temperature before it was cooled to -40 °C. To the cooled solution was added 18.20 mL of MeMgBr (3.0 M solution in Et<sub>2</sub>O, 54.6 mmol) and stirring was continued for 20 min at -40 °C followed by 10 min stirring at 0 °C. The reaction was poured into ice and diluted with Et<sub>2</sub>O (200 mL). The aqueous layer was partitioned several times with Et<sub>2</sub>O (500 mL total), and the combined Et<sub>2</sub>O extracts were washed twice with saturated aqueous NaHCO<sub>3</sub>, once with brine, and dried over MgSO<sub>4</sub>. Filtration was followed by removal of solvent under reduced pressure, and the crude residue was purified by silica gel chromatography (gradient elution, 0→30% EtOAc/Hexanes) to give 3.75 g **54** (96% yield) as a white powder.

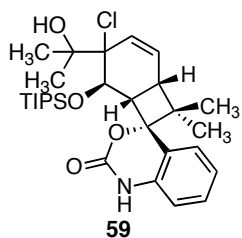
**Alcohol 54:** FTIR (NaCl/thin film) 3257 (w, br), 2942 (s), 2866 (s), 1719 (s), 1597 (m), 1488 (w), 1370 (m), 1255 (w), 1078 (m), 1054 (m), 910 (w), 733 (m), 679 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.81 (s, 1H), 7.24 (m, 2H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.77 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.06 (d, *J* = 5.6 Hz, 1H), 5.05 (d, *J* = 1.6 Hz, 1H), 3.64 (dd, *J* = 10.0, 2.4 Hz, 1H), 2.86 (brs, 1H), 2.43 (ddd, *J* = 16.4, 7.6, 2.4 Hz, 1H), 2.27 (dd, *J* = 10.0, 7.2 Hz, 1H), 2.15 (dd, *J* = 16.4, 7.6 Hz, 1H), 1.57 (s, 3H), 1.42 (s, 3H), 1.08 (m, 24H), 0.61 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 153.7, 148.0, 135.1, 129.1, 125.0, 123.1, 123.0, 121.9, 114.5, 87.8, 72.2, 63.0, 45.9, 44.1, 37.2, 29.8, 29.3, 28.5, 22.1, 19.2, 18.6, 18.5, 13.5; HRMS (ES<sup>+</sup>) calc'd for C<sub>29</sub>H<sub>45</sub>NO<sub>4</sub>SiNa [M+Na]<sup>+</sup> 522.3016, found 522.3016.

### Preparation of chloro-ketone **56**.



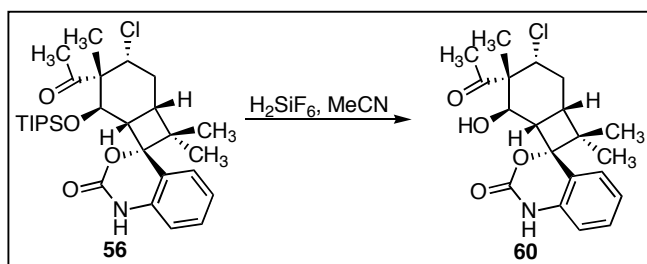
To a vigorously stirring solution of alcohol **54** (0.80 g, 1.60 mmol) dissolved in 80 mL MeCN and 14 mL CH<sub>2</sub>Cl<sub>2</sub> was added CeCl<sub>3</sub>·7H<sub>2</sub>O (1.26 g, 3.52 mmol) while stirring in a flask open to air. The mixture was cooled to −5 °C and aqueous NaOCl (diluted to ~0.1 M from commercial Clorox® (~0.84M), 19.0 mL, 19.0 mmol) was added dropwise over 5 min. The reaction temperature was maintained at −5 °C for 30 min, after which time TLC indicated the reaction was not complete and additional NaOCl was added (2 x 7.0 mL, 14.0 mmol total) and stirring continued for 1½ h total. The reaction was quenched with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and diluted with 150 mL EtOAc. The aqueous layer was partitioned with EtOAc (300 mL total), and the combined EtOAc extracts were washed once with saturated aqueous NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure, and the residue was purified by silica gel chromatography (gradient elution, 0→30% EtOAc/Hexanes) to give 0.667 g (78% yield) of **56** as a white foam.

**Chloro Ketone 56:** FTIR (NaCl/thin film): 3258 (w, br), 3166 (w), 3103 (w), 2945 (m), 2866 (m), 1719 (s), 1598 (m), 1463 (m), 1353 (m), 1260 (m), 1118 (m), 911 (m), 883 (m), 734 (m), 680 (m) cm<sup>−1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.19 (m, 1H), 7.25 (m, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 5.45 (d, *J* = 8.8 Hz, 1H), 3.87 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.53 (m, 1H), 2.33 (s, 3H), 2.03 (m, 2H), 1.48 (s, 3H), 1.25 (s, 3H), 0.87 (m, 22H), 0.76 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 208.5, 153.0, 134.9, 129.4, 125.5, 122.8, 120.7, 114.4, 89.0, 69.3, 62.6, 57.6, 46.8, 42.0, 39.1, 31.0, 29.8, 27.1, 20.1, 19.2, 18.5, 18.4, 13.8; HRMS (ES<sup>+</sup>) calc'd for C<sub>29</sub>H<sub>45</sub>NO<sub>4</sub>SiCl [M+H] 534.2806, found 534.2820.



**59**: FTIR (NaCl/thin film) 3478 (m, br), 3258 (m, br), 2944 (m), 2866 (m), 1719 (s), 1598 (m), 1462 (m), 1353 (m), 1118 (m), 734 (m), 680 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27 (brs, 1H), 7.38 (d,  $J = 8.0$  Hz, 1H), 7.30 (dt,  $J = 8.0, 1.5$  Hz, 1H), 7.18 (t,  $J = 7.5$  Hz, 1H), 6.85 (d,  $J = 8.0$  Hz, 1H), 6.09 (d,  $J = 9.0$  Hz, 1H), 5.80 (dd,  $J = 9.5, 3.5$  Hz, 1H), 5.37 (d,  $J = 8.0$  Hz, 1H), 4.54 (brs, 1H), 3.53 (dd,  $J = 10.0, 8.5$  Hz, 1H), 2.83 (ddd,  $J = 10.0, 2.5, 2.5$  Hz, 1H), 1.50 (s, 3H), 1.47 (s, 3H), 1.18 (s, 3H), 0.97 (m, 21H), 0.70 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  151.6, 134.4, 130.5, 129.5, 129.1, 124.6, 123.6, 122.2, 114.2, 85.5, 72.2, 47.9, 44.5, 40.9, 26.9, 26.24, 26.15, 20.9, 18.8, 18.5, 14.6; HRMS (ES $^{+}$ ) calc'd for  $\text{C}_{29}\text{H}_{45}\text{NO}_4\text{SiCl}$   $[\text{M}+\text{H}]^{+}$  534.2806, found 534.2832.

#### Preparation of ketone **60**.

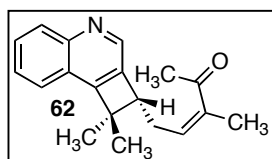


To a solution of TIPS ether **56** (1.2 g, 2.25 mmol) dissolved in 120 mL MeCN in a 250 mL plastic nalgene screw-top bottle was added 1.94 mL of aqueous  $\text{H}_2\text{SiF}_6$  (~20% wt solution, 2.70 mmol). The bottle cap was screwed tight and the reaction mixture was heated to 65  $^{\circ}\text{C}$  for 10 h. To the cooled reaction was added 200 mL EtOAc, and 100 mL saturated aqueous  $\text{NaHCO}_3$ . The aqueous wash was partitioned several times with EtOAc (400 mL total), and the combined EtOAc extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude solid was routinely used without further purification, however analytically pure **60** could be obtained by silica gel chromatography (gradient elution, 1 $\rightarrow$ 6% MeOH/ $\text{CH}_2\text{Cl}_2$ ).

**Ketone 60**: FTIR (KBr pellet): 3218 (m, br), 3143 (m,br), 2964 (m), 2944 (m), 1708 (s), 1690 (s), 1595 (m), 1490 (m), 1347 (s), 1262 (m), 1169 (w), 1060 (m), 921 (w), 750 (m)  $\text{cm}^{-1}$ ;

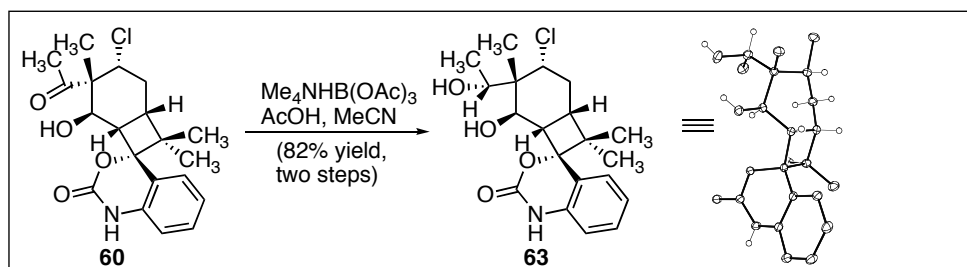


Melting point: 224 (decomposition);  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  10.17 (s, 1H), 7.45 (d,  $J$  = 7.5 Hz, 1H), 7.26 (dt,  $J$  = 7.5, 1.0 Hz, 1H), 7.08 (dt,  $J$  = 7.5, 1.0 Hz, 1H), 6.88 (dd,  $J$  = 7.5, 1.0 Hz, 1H), 4.96 (dd,  $J$  = 10.0, 6.0 Hz, 1H), 4.75 (d,  $J$  = 6.0 Hz, 1H), 4.02 (dd,  $J$  = 11.5, 4.5 Hz, 1H), 3.05 (dd,  $J$  = 10.0, 10.0 Hz, 1H), 2.23 (m, 4H), 2.06 (m, 1H), 1.90 (ddd, 12.5, 6.5, 5.0 Hz, 1H), 1.27 (s, 3H), 1.16 (s, 3H), 0.60 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$ : 209.3, 151.2, 135.7, 128.7, 125.4, 122.0, 121.7, 113.6, 85.9, 66.3, 63.1, 56.1, 46.1, 36.6, 29.8, 29.3, 26.6, 19.4, 17.5; LRMS (ES+) calc'd for  $\text{C}_{20}\text{H}_{24}\text{ClNO}_4\text{Na}$   $[\text{M}+\text{Na}]^+$  400.13, found 400.12.



**Quinoline 62:** FTIR (NaCl/thin film) 2955 (m), 2924 (m), 1667 (s), 1365 (w), 1277 (m), 763 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.64 (s, 1H), 8.14 (d,  $J$  = 10.5 Hz, 1H), 7.68 (m, 2H), 7.55 (dt,  $J$  = 10.5, 1.5 Hz, 1H), 6.84 (dt,  $J$  = 9.0, 1.5 Hz, 1H), 3.48 (dd,  $J$  = 11.5, 9.0 Hz, 1H), 2.69 (m, 2H), 2.41 (s, 3H), 1.83 (s, 3H), 1.64 (s, 3H), 1.55 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  200.0, 147.9, 145.1, 140.9, 139.2, 137.7, 131.3, 129.2, 129.1, 127.3, 124.0, 123.1, 53.7, 49.5, 30.0, 27.4, 26.1, 22.2, 12.0; HRMS (ES+) calc'd for  $\text{C}_{19}\text{H}_{22}\text{NO}$   $[\text{M}+\text{H}]^+$  280.1701, found 280.1698.

### Preparation of diol 63.

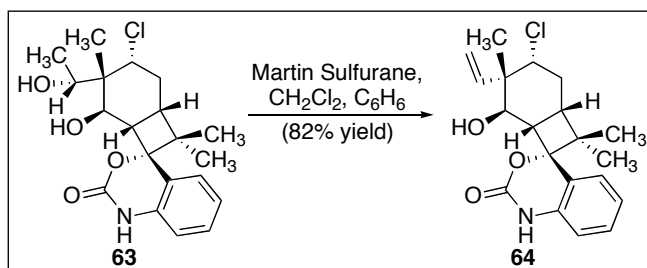


To a solution of  $\text{Me}_4\text{NHB}(\text{OAc})_3$  (4.16 g, 15.84 mmol) in 8 mL of MeCN was added 8 mL of glacial AcOH under  $\text{N}_2$ , and the resulting solution was stirred 30 min at room temperature, after which time it was added via cannula to a stirring suspension of crude ketone **60** (~2.25 mmol) dissolved in 8.0 mL MeCN. The reaction mixture was stirred for 3 h at room temperature then quenched by addition of 25 mL Rochelle's salt solution and dilution with EtOAc. The resulting biphasic mixture was stirred vigorously for 1 hr before the aqueous layer was partitioned with a total of 400 mL EtOAc. The combined EtOAc extracts were rinsed once with saturated aqueous  $\text{NaHCO}_3$ , and the aqueous wash was back extracted with EtOAc (2 x 50 mL). The EtOAc extracts were washed once more with saturated aqueous  $\text{NaHCO}_3$ , once with brine

and dried over  $\text{MgSO}_4$ . Filtration was followed by concentration under reduced pressure, and the crude solid was purified by silica gel chromatography (gradient elution, 1 $\rightarrow$ 6%  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ) to give 0.705g (82% yield over 2 steps) of **63** as a white powder. Solid **63** could be recrystallized from  $\text{CDCl}_3$  to give crystals suitable for single crystal x-ray diffraction.

**Diol 63:** melting point, 211-212  $^\circ\text{C}$  (decomposition); FTIR (NaCl/thin film) 3390 (m, br), 3251 (m, br), 2961 (m), 1715 (s), 1597 (m), 1491 (w), 1461 (w), 1355 (m), 1071 (m), 909 (w), 734 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{MeOH-d}_4$ : $\text{C}_6\text{D}_6$ , 6:1)  $\delta$  7.45 (d,  $J$  = 7.5 Hz, 1H), 7.29 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 7.16 (dd,  $J$  = 7.5, 1.5 Hz, 1H), 6.89 (dd,  $J$  = 8.0, 0.5 Hz, 1H), 4.98 (d,  $J$  = 11.0 Hz, 1H), 4.12 (dd,  $J$  = 10.5, 4.5 Hz, 1H), 4.04 (q,  $J$  = 6.5 Hz, 1H), 3.10 (dd,  $J$  = 10.5, 10.5 Hz, 1H), 2.24 (m, 1H), 2.15 (m, 1H), 1.93 (ddd,  $J$  = 13.0, 8.5, 4.5 Hz, 1H), 1.50 (d,  $J$  = 6.5, 3H), 1.35 (s, 3H), 1.18 (s, 3H), 0.60 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{MeOH-d}_4$ : $\text{C}_6\text{D}_6$ , 6:1)  $\delta$  154.6, 136.8, 130.0, 125.9, 124.2, 123.9, 115.0, 86.9, 74.8, 67.8, 66.5, 48.4, 45.9, 42.7, 38.0, 30.1, 27.5, 21.4, 19.9, 18.5; HRMS (ES $^+$ ) calc'd for  $\text{C}_{20}\text{H}_{27}\text{ClNO}_4$   $[\text{M}+\text{H}]^+$  308.1629, found 308.1629.

#### Preparation of alcohol 64.

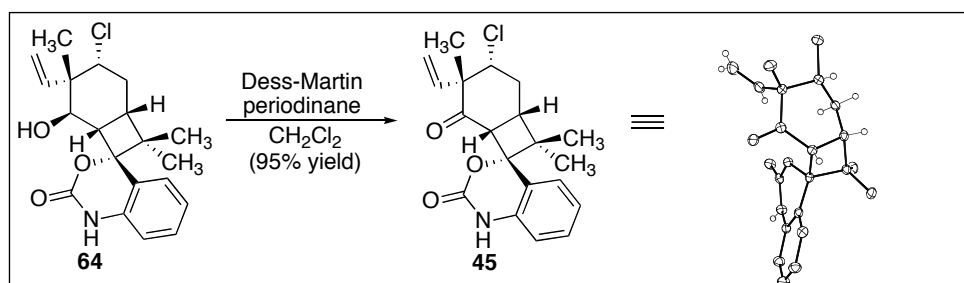


To a stirring suspension of diol **63** (230.0 mg, 0.605 mmol) in 4 mL of  $\text{CH}_2\text{Cl}_2$  and 2 mL  $\text{C}_6\text{H}_6$  under  $\text{N}_2$  was added a solution of Martin sulfurane (1.22 g, 1.81 mmol) in 4 mL benzene (note: Martin sulfurane was weighed and stored in a glove box to preserve the integrity of the reagent). The resulting yellow solution was stirred 20 min at room temperature, and then quenched with 10 mL of 0.5 M NaOH. The aqueous layer was partitioned with 400 mL total of EtOAc, and the combined EtOAc extracts were washed once with brine, dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (gradient elution, 10 $\rightarrow$ 70% EtOAc/Hexanes) to give 180.0 mg (82% yield) of **64** as a fine white powder.

**Alcohol 64:** FTIR (NaCl/thin film): 3422 (m, br), 3245 (m, br), 3096 (m), 2960 (m), 1719 (s), 1598 (m), 1492 (m), 1355 (m), 1260 (w), 1064 (m), 912 (m), 754 (m), 733 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$

NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.30 (s, 1H), 7.28 (d,  $J = 7.5$  Hz, 1H), 7.23 (t,  $J = 7.5$  Hz, 1H), 7.12 (t,  $J = 7.5$  Hz, 1H), 6.87 (d,  $J = 8.0$  Hz, 1H), 6.12 (dd,  $J = 17.5, 10.5$  Hz, 1H), 5.27 (d,  $J = 11.5$  Hz, 1H), 5.17 (d,  $J = 17.5$  Hz, 1H), 4.62 (dd,  $J = 10.5, 3.5$  Hz, 1H), 3.86 (dd,  $J = 11.0, 4.5$  Hz, 1H), 3.04 (dd,  $J = 10.0, 9.5$  Hz, 1H), 2.17 (m, 2H), 2.10 (d,  $J = 3.5$  Hz, 1H), 1.94 (m, 1H), 1.36 (s, 3H), 1.21 (s, 3H) 0.65 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.5, 141.8, 135.0, 129.3, 124.5, 123.5, 122.0, 114.6, 114.5, 86.5, 69.5, 65.4, 47.7, 46.2, 40.7, 37.5, 28.6, 27.4, 20.8, 17.0; HRMS (ES+) calc'd for  $\text{C}_{20}\text{H}_{25}\text{ClNO}_3$   $[\text{M}+\text{H}]^+$  362.1523, found 362.1521.

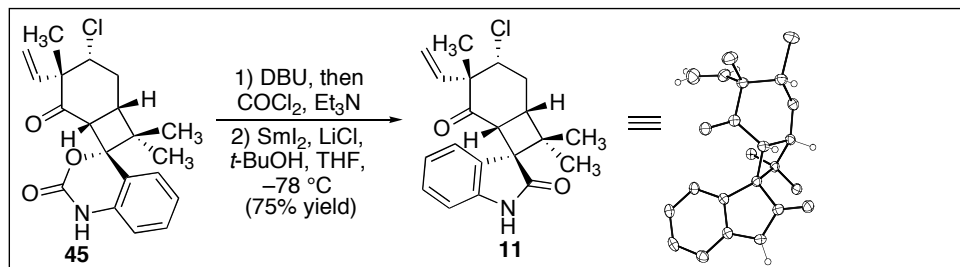
### Preparation of ketone 45.



To a stirring solution of **64** (484 mg, 1.33 mmol) in 12 mL of  $\text{CH}_2\text{Cl}_2$  was added Dess-Martin periodinane (1.35 g, 3.18 mmol) at room temperature. The resulting solution was stirred 1.5 h, after which time 12 mL saturated  $\text{Na}_2\text{S}_2\text{O}_3$  was added and the mixture was stirred until both layers were clear. Saturated  $\text{NaHCO}_3$  was added and the aqueous layers were partitioned with 400 mL total of  $\text{CH}_2\text{Cl}_2$ . The combined  $\text{CH}_2\text{Cl}_2$  extracts were washed once with brine, dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The crude solid was purified by silica gel chromatography (gradient elution, 10 $\rightarrow$ 40% EtOAc/Hexanes) to give 460 mg of **45** (95% yield) as a white powder.

**Ketone 45:** FTIR (NaCl/thin film): 3244 (w, br), 3160 (w, br), 3100 (w, br), 2958 (w), 2921 (m), 1725 (s), 1597 (m), 1492 (w), 1351 (m), 1261 (m), 1055 (m), 760 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  7.82 (s, 1H), 7.29 (t,  $J = 7.6$  Hz, 1H), 7.26 (d,  $J = 7.6$  Hz, 1H), 7.11 (t,  $J = 7.6$  Hz, 1H), 6.77 (d,  $J = 8.0$  Hz, 1H), 6.37 (dd,  $J = 17.2, 10.8$  Hz, 1H), 5.35 (d,  $J = 10.8$  Hz, 1H), 5.28 (d,  $J = 17.2$  Hz, 1H), 4.12 (dd,  $J = 13.2, 2.4$  Hz, 1H), 3.83 (d,  $J = 8.0$  Hz, 1H), 2.89 (m, 1H), 2.33 (m, 2H), 1.40 (s, 3H), 1.23 (s, 3H), 0.86 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  208.1, 152.1, 135.6, 135.1, 130.2, 126.4, 123.5, 119.4, 118.1, 114.7, 94.2, 65.3, 57.8, 48.0, 44.8, 39.7, 31.7, 27.0, 22.3, 18.5; HRMS (ES+) calc'd for  $\text{C}_{20}\text{H}_{23}\text{ClNO}_3$   $[\text{M}+\text{H}]^+$  360.1366, found 360.1374.

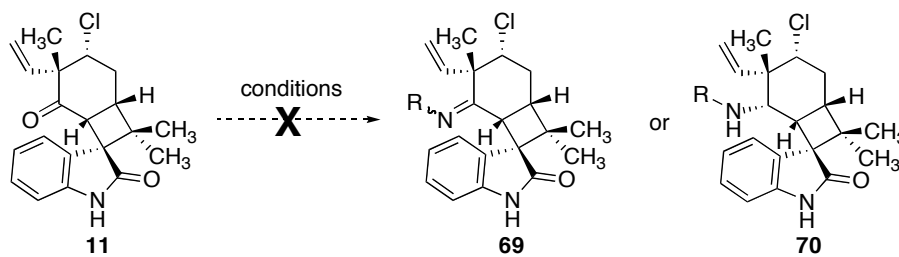
### Preparation of oxindole 11.



To a stirring solution of ketone **45** (35 mg, 0.097 mmol) in 0.7 mL THF under N<sub>2</sub> was added DBU (7  $\mu$ L, 0.047 mmol). The resulting orange solution was stirred 4 h at room temperature, at which time TLC indicated complete conversion to the aniline. The solution was cooled to 0 °C and addition of Et<sub>3</sub>N (82  $\mu$ L, 0.584 mmol) was followed by phosgene addition (287  $\mu$ L of ~20% soln in PhMe, 0.584 mmol). The mixture was warmed to room temperature over 30 min and concentrated *in vacuo* to approximately one third the original volume. The amine salts were suspended in dry Et<sub>2</sub>O (2 mL), filtered *in vacuo* over Celite (mixture transferred to a fritted filter containing Celite fitted with a rubber septa via Teflon cannula), and rinsed with a total of 25 mL dry Et<sub>2</sub>O. The filtrate was concentrated under reduced pressure, the residue was azeotroped with benzene (2 x 2 mL), and further dried *in vacuo* for 2 h. The yellow oil was dissolved in 0.5 mL THF, cooled to -78 °C while under N<sub>2</sub>, and *t*-BuOH (9  $\mu$ L, 0.097 mmol) was added. Meanwhile, in a separate flask, LiCl (65 mg, 1.55 mmol) was rapidly flame-dried *in vacuo*. Once cooled, freshly prepared SmI<sub>2</sub> (3.88 mL of ~0.1M soln, 0.388 mmol) was added rapidly and the resulting emerald green mixture was stirred 10 min under N<sub>2</sub> (note: SmCl<sub>2</sub> is only sparingly soluble in THF, therefore it should not be prepared and stored, but instead used immediately). The preformed mixture of SmI<sub>2</sub>/LiCl was added dropwise via Teflon cannula to the cooled solution of the isocyanate and stirred 15 min at -78 °C. If the reaction was not complete, additional SmI<sub>2</sub>/LiCl solution was added in 1 equivalent portions until TLC indicated no remaining isocyanate. The reaction was quenched by treating with O<sub>2</sub> at -78 °C followed by addition of saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and dilution with EtOAc. The aqueous layer was partitioned with EtOAc (50 mL total), and the combined organic extracts were washed once with saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, once with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude yellow oil was purified by silica gel chromatography (gradient elution, 10 $\rightarrow$ 30%

EtOAc/Hexanes) to give 25 mg of **11** (75% yield) as a white powder. Attempts to recrystallize from CH<sub>2</sub>Cl<sub>2</sub>/MeOH provided a single crystal suitable for x-ray diffraction.

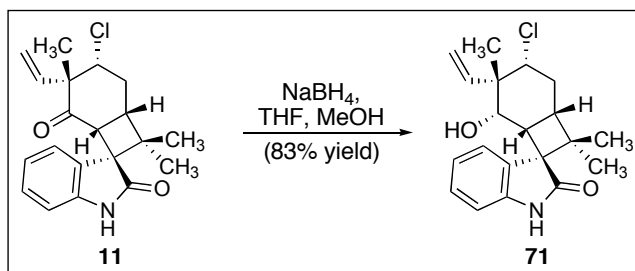
**Oxindole 11:** FTIR (NaCl/thin film) 3259 (m, br), 2965 (s), 2934 (s), 2250 (w), 1703 (s), 1698 (s), 1619 (m), 1469 (s), 1334 (m), 1297 (m), 1212 (m), 1143 (w), 1076 (w), 911 (m), 735 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.09 (brs, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 7.5, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 6.21 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.53 (d, *J* = 17.5 Hz, 1H), 5.50 (d, *J* = 10 Hz, 1H), 4.20 (dd, *J* = 9.5, 7.0, 1H), 3.43 (m, 2H), 2.23 (m, 2H), 1.41 (s, 3H), 1.11 (s, 3H), 1.04 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 208.7, 180.5, 141.3, 134.9, 128.9, 128.5, 125.2, 121.4, 119.2, 109.6, 63.2, 58.2, 57.2, 46.1, 44.2, 38.9, 28.9, 25.1, 24.3, 23.2; HRMS (ES<sup>+</sup>) calc'd for C<sub>20</sub>H<sub>23</sub>ClNO<sub>2</sub> [M+H]<sup>+</sup> 344.1417, found 344.1412.



**Table S2.** *N*-Nucleophiles screened for condensation with ketone **11**.

entry	conditions	result
1	HONH <sub>2</sub> ·HCl, pyr, 80 to 150 °C	no reaction; decomp. >150 °C
2	HONH <sub>2</sub> ·HCl, NaOAc, MeOH, Δ	no reaction
3	HONH <sub>2</sub> ·HCl, NaOAc, EtOH, Δ	no reaction
4	TMSONHTMS, KH, -78 °C to rt	no reaction
5	NH <sub>3</sub> /MeOH, Ti(O <i>i</i> -Pr) <sub>4</sub>	no reaction
6	MeClAlNH <sub>2</sub> , benzene, 55 °C	no reaction
7	H <sub>2</sub> NNH <sub>2</sub> , Sc(OTf) <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub>	no reaction
8	allyl amine, Me <sub>3</sub> Al, benzene, Δ	no reaction
9	NH <sub>4</sub> OAc, NaBH <sub>3</sub> CN, MeOH/THF, 65 to 150 °C	no reaction

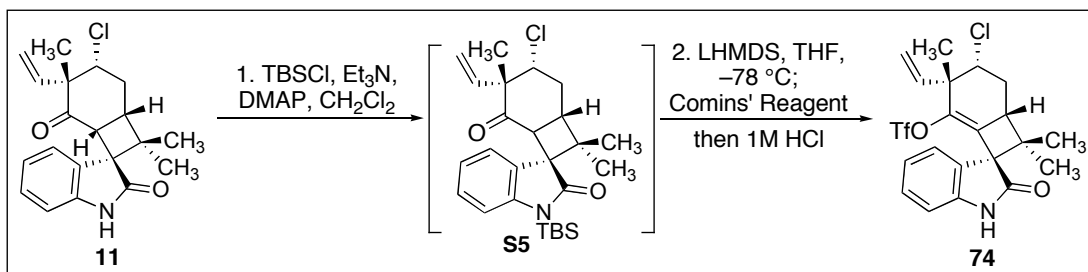
### Preparation of alcohol **71**.



To a solution of ketone **11** (12.0 mg, 0.035 mmol) dissolved in THF (0.5 mL) was added MeOH (30.0  $\mu\text{L}$ ) and  $\text{NaBH}_4$  (20 mg, 0.526 mmol). The reaction was stirred at room temperature for 1 h, after which time EtOAc (10 mL) was added followed by  $\text{H}_2\text{O}$  (5 mL). The aqueous layer was partitioned several times with EtOAc (50 mL) and the combined organic layers were washed once with brine and dried over  $\text{MgSO}_4$ . Filtration was followed by concentration under reduced pressure and silica gel chromatography (gradient elution, 0  $\rightarrow$  30% EtOAc/benzene) to give pure **71** (10.0 mg, 83% yield) as a white powder.

**Alcohol 71:** FTIR (NaCl/thin film) 3384 (m, br), 3247 (m, br), 2926 (m), 1696 (s), 1617 (m), 1468 (s), 1327 (m), 1151 (w), 751 (m), 694 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (d,  $J = 8.0$  Hz, 1H), 7.67 (brs, 1H), 7.17 (t,  $J = 7.5$  Hz, 1H), 6.93 (t,  $J = 7.5$  Hz, 1H), 6.80 (d,  $J = 7.0$  Hz, 1H), 6.44 (dd,  $J = 17.5, 11.0$  Hz, 1H), 5.34 (d,  $J = 11.0$  Hz, 1H), 5.15 (d,  $J = 18.0$  Hz, 1H), 3.79 (d,  $J = 11.5$  Hz, 1H), 3.72 (s, 1H), 2.97 (brs, 2H), 2.67 (m, 1H), 2.41 (brs, 1H), 1.87 (d,  $J = 11.5$  Hz, 1H), 1.33 (s, 3H), 1.17 (s, 6H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) 141.8, 141.3, 130.8, 127.8, 127.6, 121.6, 115.0, 109.3, 76.5, 66.5, 46.7, 45.1, 42.1, 39.7, 29.3, 27.2, 23.4, 21.3 (short 2 carbons), HRMS (ES $^+$ ) calc'd for  $\text{C}_{20}\text{H}_{25}\text{NO}_2\text{Cl}$   $[\text{M}+\text{H}]^+$  346.1574, found 346.1597.

### Preparation of vinyl triflate **74**.



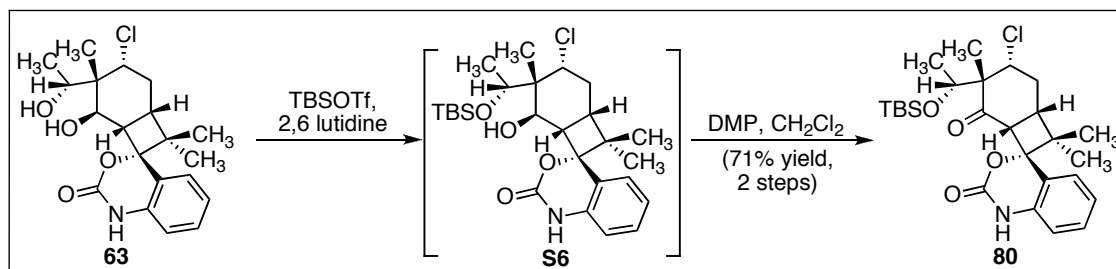
To a solution of ketone **11** (9.0 mg, 0.026 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) was added TBS chloride (80.0 mg, 0.52 mmol),  $\text{Et}_3\text{N}$  (91.0  $\mu\text{L}$ , 0.65 mmol) and DMAP (0.5 mg, 0.004 mmol).

The flask was sealed with a glass stopper and heated to 40 °C in a sand bath overnight. The reaction was stopped by concentration under reduced pressure and the residue was purified by silica gel chromatography (gradient elution, 0 → 10% EtOAc/Hexanes) to give 10 mg (84% yield) of **S5** as colorless oil. The *N*-TBS compound was not stable to storage, therefore it was immediately used in the subsequent step.

To a solution of **S5** (10.0 mg, 0.022 mmol) in dry THF (1mL) cooled to –40 °C under N<sub>2</sub> was added LHMDS (1M solution in THF, 0.20 mL, 0.20 mmol). The reaction was stirred for 45 min at this temperature, after which time a solution of Comins' reagent (78.0 mg, 0.20 mmol, solution in 0.3 mL THF) was added via canula. After stirring an additional 1 h at –40 °C, the reaction was quenched by addition of saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was partitioned with EtOAc (50 mL total) and the combined organic layers were washed once with brine and concentrated under reduced pressure. The residue was taken up in THF (1 mL) and 1M HCl was added (0.1 mL). The reaction was stirred for 20 min, then partitioned with EtOAc (50 mL total). The combined organic layers were washed once with saturated aqueous NaHCO<sub>3</sub> and dried over MgSO<sub>4</sub>. Filtration followed by concentration under reduced pressure and silica gel chromatography provided **74** (7 mg, 67 % yield) as a white powder.

**Vinyl Triflate 74:** FTIR (NaCl/thin film) 1711 (m), 1622 (w), 1470 (w), 1422 (w), 1211 (s), 1138 (w), 1029 (w), 848 (w) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49 (brs, 1H), 7.26 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.02 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 5.98 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.45 (d, *J* = 10.8 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 4.13 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.65 (dd, *J* = 10.8, 6.8 Hz, 1H), 2.01 (m, 1H), 1.58 (s, 3H), 1.41 (s, 3H), 1.26 (s, 3H), 1.74 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 176.4, 114.9, 139.4, 138.3, 129.4, 127.7, 126.4, 123.9, 122.0, 118.6 (q, triflate carbon), 118.0, 109.9, 64.9, 64.4, 48.0, 47.6, 46.1, 29.2, 23.7, 21.7, 20.7; HRMS (ES<sup>+</sup>) calc'd for C<sub>21</sub>H<sub>22</sub>NO<sub>4</sub>ClF<sub>3</sub>S [M+H]<sup>+</sup> 476.0910, found 476.0903.

#### Preparation of ketone **80**.

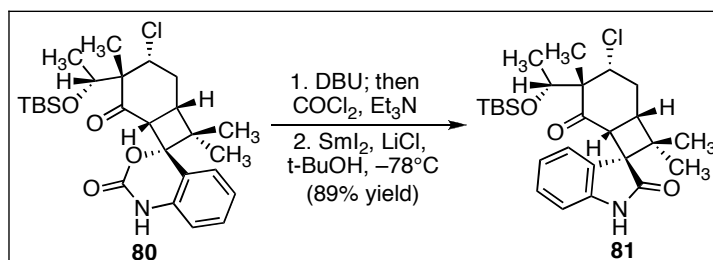


To a suspension of diol **63** (352.0 mg, 0.926 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under N<sub>2</sub> was added 2,6 lutidine (1.08 mL, 9.26 mmol) followed by TBSOTf (1.77 mL, 2.32 mmol) at room temperature. The reaction was stirred 30 min, then quenched by addition of 1M HCl (10 mL). The aqueous layer was partitioned with CH<sub>2</sub>Cl<sub>2</sub> (150 mL total) and the combined organic layers were washed once more with 1 M HCl (20 mL), once with saturated aqueous NaHCO<sub>3</sub> (20 mL), once with brine (20 mL) and dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure and silica gel chromatography (10 → 30% EtOAc/Hexanes) to give pure **S6** (438.0 mg, 96% yield) as a colorless oil.

To a solution of silyl ether **S6** (438 mg, 0.890 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added DMP (1.24 g, 2.67 mmol). The reaction was stirred at room temperature for 2 h then quenched by addition of saturated sodium thiosulfate, diluted with 10 mL CH<sub>2</sub>Cl<sub>2</sub>, and vigorously stirred until both layers were clear. Saturated aqueous NaHCO<sub>3</sub> was added, the aqueous layer was partitioned with CH<sub>2</sub>Cl<sub>2</sub> (200 mL total), and the combined organic extracts were dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure and silica gel chromatography (gradient elution, 0 → 30 % EtOAc/Hexanes) to give **80** (325 mg, 74% yield, 71% yield over 2 steps from **63**) as a white powder.

**Ketone 80:** FTIR (NaCl/thin film) 3225 (m, br), 3164 (m, br), 3104 (m, br), 2956 (m), 2928 (m), 1716 (s), 1598 (m), 1351 (m), 1256 (m), 1077 (m), 836 (m), 776 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.95 (s, 1H), 7.23 (dt, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.05 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.71 (q, *J* = 6.0 Hz, 1H), 4.49 (*J* = dd, *J* = 5.0, 5.0 Hz, 1H), 3.91 (d, *J* = 10.0 Hz, 1H), 2.63 (m, 2H), 2.52 (ddd, *J* = 17.0, 12.0, 5.5 Hz, 1H), 1.35 (s, 3H), 1.27 (s, 3H), 1.19 (d, *J* = 5.5 Hz, 3H) 0.91 (s, 9H), 0.78 (s, 3H), 0.16 (s, 3H), 0.13 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 207.4, 152.9, 135.2, 129.5, 125.4, 122.9, 120.1, 114.7, 90.7, 67.8, 63.7, 57.3, 47.6, 44.6, 40.1, 29.1, 28.2, 26.2, 20.5, 19.6, 18.2, 15.2, -3.6, -4.3; HRMS (ES+) calc'd for C<sub>26</sub>H<sub>39</sub>ClNO<sub>4</sub>Si [M+H]<sup>+</sup> 492.2337, found 492.2353.

#### Preparation of oxindole **81**.



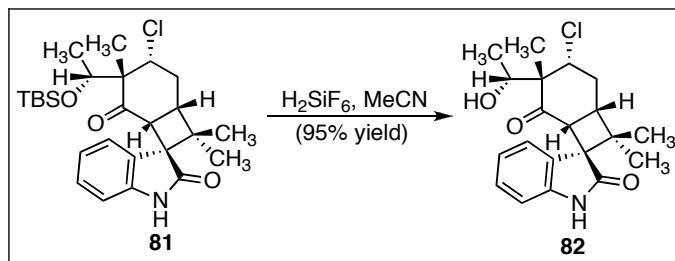


To a solution of ketone **80** (22.0 mg, 0.045 mmol) in THF (0.5 mL) was added DBU (7.0  $\mu$ L, 0.040 mmol) and the resulting yellow-orange solution was stirred for 8 h at room temperature, after which time TLC indicated consumption of the starting material. The solution was cooled to 0 °C and Et<sub>3</sub>N (63.0  $\mu$ L, 0.450 mmol) and phosgene (~20% solution in PhMe, 0.22 mL, 0.450 mmol) were sequentially added. The reaction was stirred 30 min at 0 °C then warmed to room temperature and concentrated to one half the volume *in vacuo*. Upon dilution with dry Et<sub>2</sub>O, the Et<sub>3</sub>N salts were removed by filtration over Celite and rinsed with dry Et<sub>2</sub>O (20 mL total). The solvent was removed under reduced pressure and the residue was dried *in vacuo* for 2 h. The dry residue was taken up in 1 mL of dry THF, cooled to -78 °C, and *t*-BuOH was added (0.5 M solution in THF, 90  $\mu$ L, 0.045 mmol).

In a separate flask, LiCl (61 mg, 1.44 mmol) was quickly flame-dried *in vacuo*. Upon cooling, SmI<sub>2</sub> (0.10 M solution in THF, 1.8 mL, 0.18 mmol) was added under N<sub>2</sub> and the resulting green mixture was vigorously stirred at room temperature. After 10 min, the green mixture was added via canula to the THF solution of the isocyanate. After stirring 20 min, TLC indicated remaining isocyanate. A second portion of SmI<sub>2</sub>/LiCl was prepared as before (61 mg LiCl, 1.8 mL SmI<sub>2</sub>) and added via canula and the reaction was stirred 20 min longer at -78 °C. The reaction was quenched by addition of aqueous saturated NH<sub>4</sub>Cl and diluted with EtOAc. The aqueous layer was partitioned with EtOAc (100 mL total) and the combined organic extracts were washed once with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, once with brine, and dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure, and the crude residue was purified by silica gel chromatography (gradient elution, 10 → 30% EtOAc/Hexanes) to give pure **81** (19 mg, 89 % yield) as a white powder.

**Oxindole 81:** FTIR (NaCl/thin film) 3498 (m, br), 2955 (m), 2929 (m), 2856 (m), 1703 (s), 1619 (m), 1470 (m), 1251 (m), 1085 (m), 835 (m), 734 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.97 (s, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.54 (q, *J* = 6.0, 1H), 3.71 (d, *J* = 12.4, 1H), 3.61 (ddd, *J* = 12.8, 10.8, 1.6 Hz, 1H), 2.65 (ddd, *J* = 17.6, 11.2, 6.4 Hz, 1H), 2.21 (d, *J* = 17.2 Hz, 1H), 1.28 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  209.5, 181.1, 141.0, 130.2, 128.0, 126.3, 121.4, 109.4, 67.7, 66.5, 58.4, 56.5, 44.7, 44.6, 43.1, 27.2, 26.9, 26.1, 24.3, 20.0, 18.2, 14.4, -3.7, -4.7; HRMS (ES<sup>+</sup>) calc'd C<sub>26</sub>H<sub>39</sub>ClNO<sub>3</sub>Si [M+H]<sup>+</sup> 476.2388, found 476.2378.

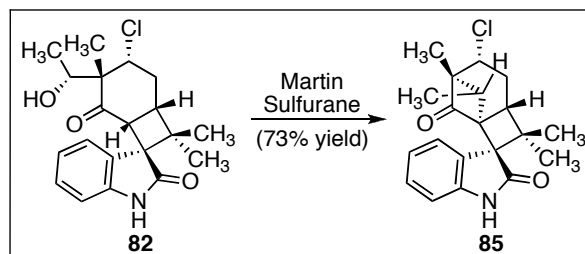
### Preparation of alcohol **82**.



To a solution of silyl ether **81** (25.0 mg, 0.053 mmol) in MeCN (2.5 mL) was added  $\text{H}_2\text{SiF}_6$  (~20% aqueous solution, 50.0  $\mu\text{L}$ , 0.069 mmol) and the mixture was heated in a sealed tube to 60 °C for 4 hrs. The reaction was concentrated under reduced pressure and the residue was purified by silica gel chromatography (gradient elution, 10  $\rightarrow$  40% EtOAc/Hexanes) to give pure **82** (18.0 mg, 95% yield) as a white powder.

**Alcohol 82:** FTIR (NaCl/thin film) 3250 (m, br), 2960 (m), 2925 (m), 2250 (w), 1702 (s), 1619 (m), 1469 (m), 910 (m), 734 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (brs, 1H), 7.42 (d,  $J = 4.5$  Hz, 1H), 7.22 (t,  $J = 7.5$  Hz, 1H), 7.05 (t,  $J = 7.5$  Hz, 1H), 6.83 (d,  $J = 7.5$  Hz, 1H), 4.43 (dd,  $J = 10.0, 4.5$  Hz, 1H), 4.23 (m, 1H), 3.62 (d,  $J = 12.0$  Hz, 1H), 3.38 (ddd,  $J = 11.5, 9.0, 9.0$  Hz, 1H), 3.26 (brs, 1H), 2.30 (m, 2H), 1.45 (d,  $J = 8.5$  Hz, 1H), 1.41 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  214.3, 180.1, 141.1, 130.0, 128.5, 125.6, 121.5, 109.5, 71.4, 64.4, 58.0, 55.7, 45.4, 44.8, 41.2, 30.6, 29.8, 25.8, 23.4, 22.3, 21.0; HRMS (ES+) calc'd for  $\text{C}_{20}\text{H}_{25}\text{NO}_3\text{Cl}$   $[\text{M}+\text{H}]^+$  362.1523, found 362.1527.

### Preparation of cyclobutanone **85**.

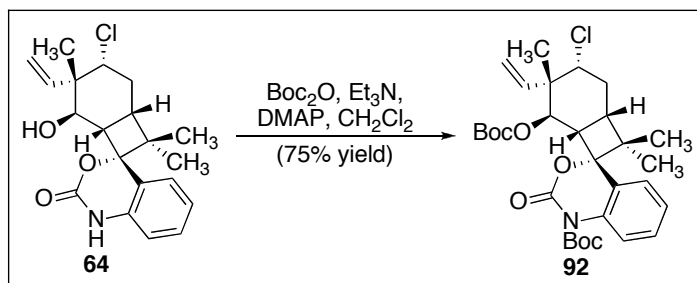


To a solution of alcohol **82** (10.0 mg, 0.028 mmol) in benzene (0.5 mL) was added Martin sulfurane (74.0 mg, 0.110 mmol; Martin sulfurane was weighed and stored in a glove box) via canula as a solution in  $\text{CH}_2\text{Cl}_2$  (0.5 mL). After stirring 20 min at room temperature, TLC indicated consumption of starting material and the reaction was quenched by addition of 1M

NaOH. The aqueous layer was partitioned with EtOAc (50 mL total) and the combined organic extracts were washed once with brine, and dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure and silica gel chromatography (gradient elution, 20 → 50% EtOAc/Hexanes) to give pure **85** (7.0 mg, 73% yield) as a white powder.

**Pentacycle 85:** FTIR (NaCl/thin film) 3285 (m, br), 2965 (m), 2929 (m), 1780 (s), 1703 (s), 1617 (m), 1469 (s), 1238 (m), 910 (m), 757 (m), 733 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.55 (brs, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.23 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.99 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.85 (d, *J* = 7.5 Hz, 1H), 4.39 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.42 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.97 (q, *J* = 7.0 Hz, 1H), 2.34 (ddd, *J* = 13.5, 6.5, 6.5 Hz, 1H), 2.23 (ddd, *J* = 13.5, 13.5, 10.0 Hz, 1H), 1.50 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 198.0, 176.3, 141.8, 128.9, 127.5, 124.6, 121.3, 109.9, 68.7, 66.5, 65.5, 58.2, 48.3, 45.8, 29.6, 29.3, 24.6, 23.4, 13.1, 12.6; HRMS (ES<sup>+</sup>) calc'd for C<sub>20</sub>H<sub>23</sub>ClNO<sub>2</sub> [M+H]<sup>+</sup> 344.1417, found 344.1400.

#### Preparation of bis-Boc derivative **92**.

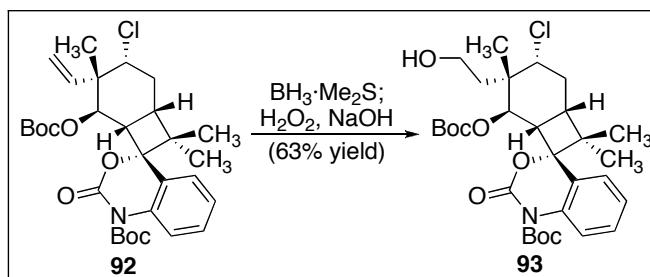


To a solution of alcohol **64** (45.0 mg, 0.124 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added Et<sub>3</sub>N (0.35 mL, 2.48 mmol) followed by Boc<sub>2</sub>O (0.29 mL, 1.24 mmol) and DMAP (0.5 mg, 0.004 mmol) while stirring under N<sub>2</sub>. The reaction was stirred at room temperature for 24 h, then quenched by addition of saturated aqueous NaHCO<sub>3</sub> (5 mL). The aqueous layer was partitioned with CH<sub>2</sub>Cl<sub>2</sub> (40 mL total) and the combined organic extracts were dried over MgSO<sub>4</sub>. Filtration followed by concentration under reduced pressure and silica gel chromatography provided pure **92** (52.0 mg, 75% yield) as a white foam.

**Bis-Boc Derivative 92:** FTIR (NaCl/thin film) 3425 (m, br), 2979 (m), 2931 (m), 1748 (s), 1459 (m), 1369 (m), 1276 (s), 1255 (S), 1148 (s), 1096 (m), 733 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.36 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.25 (dt, *J* = 7.5, 1.5 Hz, 1H), 6.21 (d, *J* = 9.5 Hz, 1H), 6.15 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.21 (d,

$J = 11.0$  Hz, 1H), 5.10 (d,  $J = 17.0$  Hz, 1H), 3.90 (dd,  $J = 10.5, 4.0$  Hz, 1H), 3.27 (dd,  $J = 9.5, 9.5$  Hz, 1H), 2.26 (m, 2H), 2.06 (m, 1H), 1.56 (s, 9 H), 1.41 (s, 3H), 1.36 (s, 9H), 1.26 (s, 3H), 0.69 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  152.0, 150.3, 148.8, 140.7, 134.5, 128.8, 128.3, 125.3, 123.6, 121.2, 114.8, 85.4, 84.8, 82.3, 73.9, 64.9, 46.9, 45.9, 38.1, 37.6, 28.9, 28.0, 27.8, 27.6, 20.3, 18.0;

### Preparation of alcohol **93**.

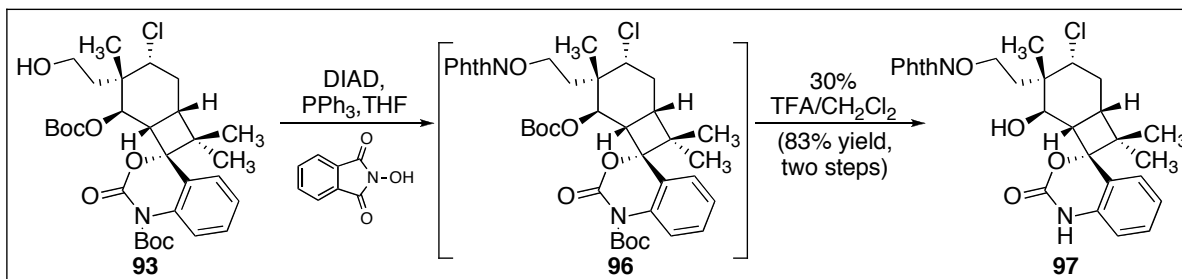


To a  $0^\circ\text{C}$  solution of bis-Boc derivative **92** (76.0 mg, 0.135 mmol) in dry THF (0.5 mL) was added  $\text{BH}_3 \cdot \text{Me}_2\text{S}$  (~10 M solution in dimethylsulfide 54.0  $\mu\text{L}$ , 0.540 mmol) under  $\text{N}_2$ . The reaction was stirred 10 h with the temperature maintained between 10 and  $15^\circ\text{C}$ , after which time pH 7 monophosphate buffer (0.3 mL) and  $\text{H}_2\text{O}_2$  (30% aqueous solution, 0.3 mL) were added. The reaction was stirred at room temperature an additional 12 h, then the aqueous layer was partitioned with EtOAc (100 mL total). The combined organic layers were washed once with brine and dried over  $\text{MgSO}_4$ . Filtration followed by concentration under reduced pressure and silica gel chromatography (gradient elution, 20  $\rightarrow$  60% EtOAc/Hexanes) provided pure **93** (49.0 mg, 63% yield) as a white foam.

**Alcohol 93:** FTIR (NaCl/thin film) 3524 (m, br), 2980 (m), 2934 (m), 1749 (s), 1459 (m), 1277 (s), 1255 (s), 1150 (s), 1093 (m), 913 (w), 774 (m), 733 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (d,  $J = 8.0$  Hz, 1H), 7.37 (dt,  $J = 8.0, 2.0$  Hz, 1H), 5.80 (d,  $J = 8.5$  Hz, 1H), 4.04 (dd,  $J = 11.0, 4.5$  Hz, 1H), 3.99 (ddd,  $J = 11.5, 7.0, 7.0$  Hz, 1H), 3.90 (ddd,  $J = 11.5$  Hz, 7.5, 5.0 Hz, 1H), 3.29 (dd,  $J = 9.0, 9.0$  Hz, 1H), 2.33 (ddd,  $J = 13.5, 10.0, 10.0$  Hz, 1H), 2.25 (ddd,  $J = 9.5, 9.5, 8.5$  Hz, 1H), 2.07 (ddd,  $J = 13.0, 8.0, 5.0$  Hz, 1H), 1.98 (m, 2H), 1.56 (s, 9H), 1.41 (s, 9H) 1.39 (s, 3H), 1.12 (s, 3H), 0.67 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.3, 150.2, 149.3, 134.4, 128.9, 128.2, 125.4, 123.7, 121.2, 85.9, 85.0, 82.8, 74.0, 65.2, 59.8, 46.9, 42.2, 38.5, 37.6,

27.5, 29.0, 28.0, 27.9, 27.9, 21.4, 20.3; HRMS (ES<sup>+</sup>) calc'd for C<sub>30</sub>H<sub>43</sub>NO<sub>8</sub>Cl [M+1]<sup>+</sup> 580.2677, found 580.2679.

### Preparation of phthalimide **97**.



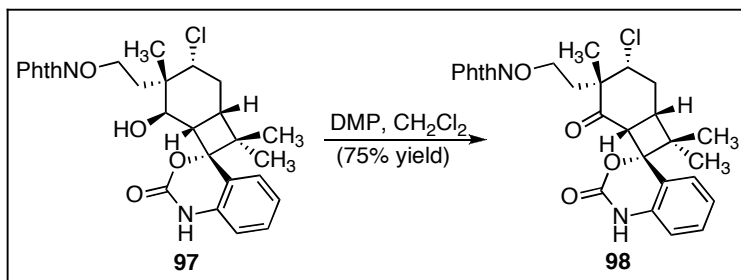
To a flask containing alcohol **93** (44.0 mg, 0.076 mmol), PPh<sub>3</sub> (75.0 mg, 0.285 mmol) and *N*-hydroxyphthalimide (62.0 mg, 0.380 mmol) under N<sub>2</sub> was added dry THF (2 mL) followed by DIAD (56.0  $\mu$ L, 0.285 mmol). The reaction immediately turned a dark orange/red color, which gradually faded over 30 min to a colorless solution. The reaction was quenched after 45 min at room temperature by addition of saturated aqueous NaHCO<sub>3</sub>. The aqueous layer was partitioned with EtOAc (50 mL total), and the combined organic extracts were washed once with brine and dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure and the crude residue was purified by silica gel chromatography (gradient elution, 20  $\rightarrow$  50% EtOAc/Hexanes) to give **96** as a white foam which was contaminated with a DIAD biproduct (total mass: 60 mg). This material was used as is in the following step.

To a solution of impure **96** (60 mg including impurity) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added TFA (1 mL) and the reaction was stirred at room temperature. After 3 hours the reaction was concentrated under reduced pressure and the crude residue was purified by silica gel chromatography (10  $\rightarrow$  50% EtOAc/Hexanes) to give pure **97** as a white powder (33.0 mg, 83% yield over 2 steps).

**Phthalimide 97:** FTIR (NaCl/thin film) 3222 (w, br), 2961 (w), 2924 (w), 1787 (w), 1729 (s), 1596 (w), 1467 (w), 1360 (w), 1186 (w), 1063 (w), 981 (w), 699 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, acetone-d<sub>6</sub>)  $\delta$  7.87 (m, 4H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 4.60 (d, *J* = 10.0 Hz, 1H), 4.53 (m, 1H), 4.26 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.22 (dd, *J* = 10.0, 10.0 Hz, 1H), 2.29 (m, 2H), 2.16 (m, 3H), 1.32 (s, 3H), 1.20 (s, 3H), 0.64 (s, 3H); <sup>13</sup>C NMR (126 MHz, acetone-d<sub>6</sub>)  $\delta$  164.2, 152.0, 151.9, 137.2, 131.1,

135.5, 130.2, 129.7, 125.9, 124.0, 123.83, 123.79, 123.3, 114.6, 114.5, 86.5, 76.7, 69.0, 68.9, 67.8, 47.9, 37.8, 36.4, 27.7, 21.1, 19.0; HRMS (ES<sup>+</sup>) calc'd for C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub>Cl [M+H]<sup>+</sup> 525.1792, found 525.1798.

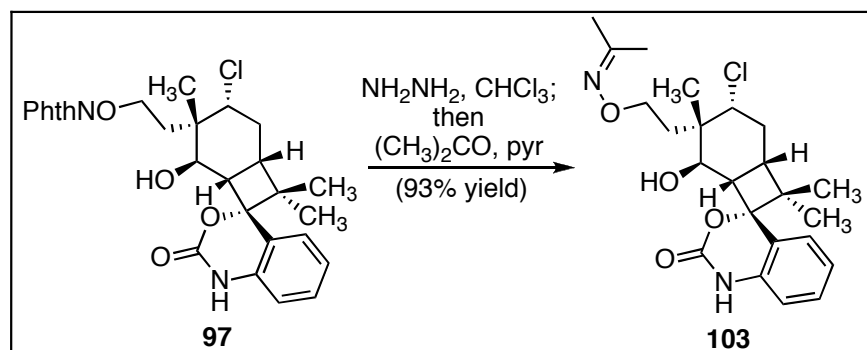
### Preparation of ketone **98**.



To a solution of alcohol **97** (2.0 mg, 0.004 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.4 mL) was added DMP (10.0 mg, 0.024 mmol). The reaction was stirred at room temperature for 40 min then quenched by addition of saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (3 mL). The biphasic mixture was stirred 30 min, then partitioned with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed once with saturated aqueous NaHCO<sub>3</sub>, once with brine, and dried over MgSO<sub>4</sub>. Filtration followed by concentration under reduced pressure and silica gel chromatography provided pure **98** (1.5 mg, 75% yield) as a white powder.

**Ketone 98:** FTIR (NaCl/thin film) 3236 (m, br), 2923 (m), 1733 (s), 1347 (w), 1054 (w), 700 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.69 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.23 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.91 (brs, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 4.40 (ddd, *J* = 9.0, 9.0, 6.0 Hz, 1H), 4.22 (ddd, *J* = 9.0, 9.0, 6.0 Hz, 1H), 4.10 (m, 1H), 3.77 (m, 1H), 2.88 (m, 1H), 2.74 (m, 1H), 2.38 (ddd, *J* = 14.0, 8.5, 8.5 Hz, 1H), 2.30 (m, 2H), 1.45 (s, 3H), 1.22 (s, 3H), 0.85 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 209.6, 163.8, 151.0, 135.0, 134.2, 129.9, 129.4, 126.1, 123.5, 123.3, 118.8, 114.5, 100.2, 93.8, 75.2, 66.0, 52.7, 47.7, 44.6, 39.3, 31.0, 29.8, 29.4, 22.7, 18.4; HRMS (ES<sup>+</sup>) calc'd for

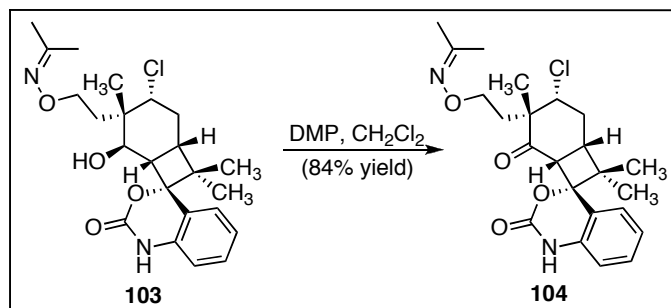
### Preparation of oxime **103**.



To a solution of phthalimide **97** (33.0 mg, 0.062 mmol) in  $\text{CHCl}_3$  (2.0 mL) was added hydrazine hydrate (50.0  $\mu\text{L}$ , 1.60 mmol) and the reaction was stirred 20 min at room temperature. After this time, white precipitate had formed and the reaction was concentrated under reduced pressure. The crude residue was taken up in acetone (1.0 mL) and pyridine (10.0  $\mu\text{L}$ , 0.124 mmol) was added. The mixture was stirred 30 min, then diluted with  $\text{CH}_2\text{Cl}_2$  and filtered through celite. The filtrate was concentrated under reduced pressure and the crude residue was purified by silica gel chromatography (gradient elution, 20  $\rightarrow$  60% EtOAc/Hexanes) to give pure **103** (25.0 mg, 93% yield) as a white powder.

**Oxime 103:** FTIR (NaCl/thin film) 3244 (m, br), 2957 (m), 2925 (m), 1720 (s), 1598 (m), 1355 (m), 1065 (m), 962 (m), 733 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.34 (brs, 1H), 7.30 (d,  $J = 7.5$  Hz, 1H), 7.26 (t,  $J = 7.5$  Hz, 1H), 7.13 (t,  $J = 7.5$  Hz, 1H), 6.82 (d,  $J = 8.0$  Hz, 1H), 4.76 (d,  $J = 10.5$  Hz, 1H), 4.35 (m, 2H), 3.95 (m, 1H), 3.03 (dd,  $J = 10.0, 10.0$  Hz, 1H), 2.13 (m, 3H), 1.99 (m, 2H), 1.93 (s, 3H), 1.91 (s, 3H), 1.36 (s, 3H), 1.12 (s, 3H), 0.62 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  155.7, 152.7, 135.1, 129.2, 124.6, 123.5, 122.6, 114.2, 86.2, 70.5, 69.1, 66.9, 47.7, 42.3, 41.5, 37.4, 36.3, 28.7, 27.4, 22.1, 21.0, 19.5, 16.0; HRMS ( $\text{ES}^+$ ) calc'd for  $\text{C}_{23}\text{H}_{32}\text{N}_2\text{O}_4\text{Cl}$   $[\text{M}+\text{H}]^+$  435.2051, found 435.2030.

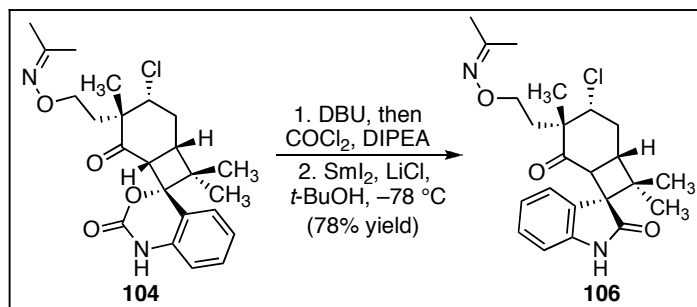
### Preparation of ketone **104**.



To a solution of alcohol **103** (25.0 mg, 0.058 mmol) in  $\text{CH}_2\text{Cl}_2$  (2.0 mL) was added DMP (74.0 mg, 0.170 mmol) and the mixture was stirred at room temperature for 2 h. After this time, the reaction was concentrated and the crude residue was purified by silica gel chromatography (gradient elution, 0  $\rightarrow$  30% EtOAc/Hexanes) to give pure **104** (21.0 mg, 84% yield) as a white powder.

**Ketone 104:** FTIR (NaCl/thin film) 3256 (m, br), 3105 (w), 2964 (s), 2875 (s), 2250 (w), 1725 (s), 1598 (m), 1502 (m), 1488 (m), 1373 (m), 1346 (m), 1261 (m), 1132 (w), 1056 (m), 913 (m), 760 (m), 732 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.79 (brs, 1H), 7.23 (m, 2H), 7.06 (dt,  $J = 8.0, 1.5$  Hz, 1H), 6.78 (d,  $J = 7.5$  Hz, 1H), 4.16 (m, 1H), 4.08 (m, 2H), 3.79 (d,  $J = 9.0$  Hz, 1H), 2.93 (ddd,  $J = 12.0, 12.0, 12.0$  Hz, 1H), 2.55 (ddd,  $J = 14.0, 8.0, 6.0$  Hz, 1H), 2.26 (m, 2H), 1.81 (s, 6H), 1.34 (s, 3H), 1.25 (s, 3H), 0.85 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) 209.6, 154.3, 152.3, 135.0, 129.8, 125.9, 123.2, 118.8, 114.7, 93.7, 69.7, 66.8, 52.9, 47.7, 44.6, 39.4, 30.9, 29.5, 27.0, 22.5, 22.0, 18.4, 15.8; HRMS (ES $^{+}$ ) calc'd for  $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_4\text{Cl}$   $[\text{M}+\text{H}]^{+}$  433.1894, found 433.1904.

### Preparation of oxindole **106**.



To a solution of oxime **104** (20.0 mg, 0.046 mmol) in THF (1.0 mL) was added DBU (6.0  $\mu\text{L}$ , 0.041 mmol) and the reaction was stirred at room temperature for 5 h. After this time, the

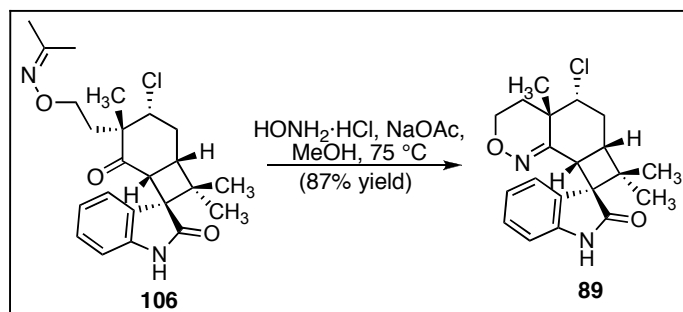


orange solution was cooled to 0 °C and DIPEA (80.0  $\mu$ L, 0.46 mmol) and phosgene (~20% solution in PhMe, 0.242 mL, 0.46 mmol) were added sequentially. After stirring 20 min at 0 °C, the mixture was warmed to room temperature, concentrated to half the volume *in vacuo* and then diluted with dry Et<sub>2</sub>O (5.0 mL). The amine salts were filtered over Celite and washed thoroughly with dry Et<sub>2</sub>O (20 mL total), and the filtrate was concentrated under reduced pressure then dried *in vacuo* for 2 h.

In a separate flask, LiCl (42.0 mg, 1.00 mmol) was quickly flame-dried *in vacuo*. Upon cooling, SmI<sub>2</sub> (0.1 M solution in THF, 2.50 mL, 0.250 mmol) was added and the emerald green mixture was rapidly stirred under N<sub>2</sub> for 10 min. Separately, the crude isocyanate residue was dissolved in dry THF (1.0 mL), cooled to -78 °C under N<sub>2</sub>, and *t*-BuOH (4.4  $\mu$ L, 0.046 mmol) was added. To the cooled solution was then added the preformed SmI<sub>2</sub>/LiCl mixture (1.84 mL, 0.184 mmol) via syringe. After 15 min, TLC indicated isocyanate still remained so a second flask of SmI<sub>2</sub>/LiCl mixture was prepared as above, of which an additional 1.84 mL (0.184 mmol) was added via syringe to the reaction mixture. The reaction was stirred 15 min longer, then quenched by addition of saturated aqueous NH<sub>4</sub>Cl. The aqueous layer was partitioned with EtOAc (40 mL total) and the combined organic extracts were washed once with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, once with brine, and dried over MgSO<sub>4</sub>. Filtration followed by concentration under reduced pressure and silica gel chromatography (gradient elution, 10  $\rightarrow$  30% EtOAc/Hexanes) provided pure **106** (15.0 mg, 78% yield) as a white solid.

**Oxindole 106:** FTIR (NaCl/thin film) 3246 (m, br), 2962 (m), 2926 (m), 1702 (s), 1619 (m), 1469 (m), 1262 (w), 1069 (m), 910 (m), 735 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.52 (brs, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.20 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.37 (ddd, *J* = 10.0, 10.0, 5.5 Hz, 1H), 4.27 (ddd, *J* = 10.0, 10.0, 5.5 Hz, 1H), 4.22 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.40 (m, 2H), 2.31 (ddd, *J* = 14.5, 9.5, 5.5 Hz, 1H), 2.19 (m, 3H), 1.90 (s, 3H), 1.89 (s, 3H), 1.28 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  209.6, 179.1, 153.8, 140.0, 128.4, 127.3, 124.3, 120.4, 108.3, 68.1, 63.7, 56.9, 51.8, 44.7, 42.8, 38.5, 31.0, 28.1, 24.2, 23.4, 22.3, 20.9, 14.8; HRMS (ES<sup>+</sup>) calc'd for C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>Cl [M+H]<sup>+</sup> 417.1945, found 417.1964.

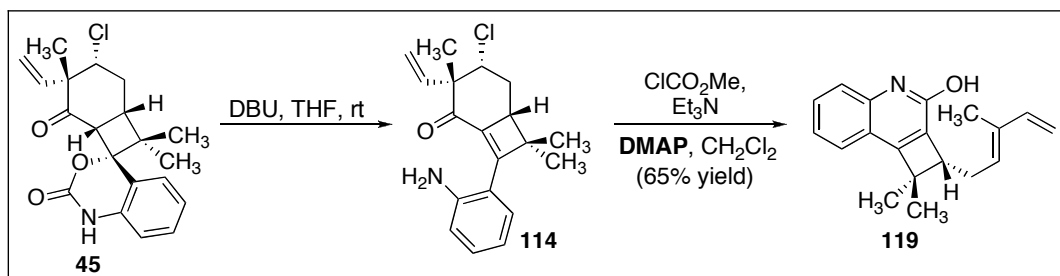
### Preparation of oxazine **89**.



To a glass microwave vessel containing **106** (8.0 mg, 0.019 mmol), HONH<sub>2</sub>·HCl (27.0 mg, 0.384 mmol), and NaOAc (32.0 mg, 0.384 mmol) was added MeOH (0.8 mL) and H<sub>2</sub>O (0.1 mL). The vessel was equipped with a stirbar, sealed, and heated to 75 °C (30 sec pre-stirring, “very high” irradiation setting) for 2 ½ h. After this time, the mixture was transferred to a flask and concentrated under reduced pressure. The residue was dissolved in EtOAc (5 mL) and H<sub>2</sub>O was added (3 mL). The aqueous layer was partitioned several times with EtOAc (30 mL total), and the combined organic extracts were washed once with brine and dried over MgSO<sub>4</sub>. Filtration was followed by concentration under reduced pressure and silica gel chromatography (gradient elution, 10 → 30% EtOAc/Hexanes) to give pure **89** (6.0 mg, 87% yield) as a white film.

**Oxazine 89**: FTIR (NaCl/thin film) 3270 (s, br), 2960 (m), 2927 (m), 1701 (s), 1617 (m), 1469 (m), 1053 (w), 747 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.77 (brs, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 4.11 (m, 2H), 4.05 (dd, *J* = 12.0, 4.0 Hz, 1H), 3.73 (d, *J* = 10.0 Hz, 1H), 3.09 (ddd, *J* = 11.5, 10.5, 7.5 Hz, 1H), 2.20 (ddd, *J* = 14.0, 10.0, 6.5 Hz, 1H), 2.05 (ddd, *J* = 13.0, 7.5, 3.5 Hz, 1H), 1.96 (m, 2H), 1.32 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H); HRMS (ES<sup>+</sup>) calc'd for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>Cl [M+H]<sup>+</sup> 359.1526, found 359.1533.

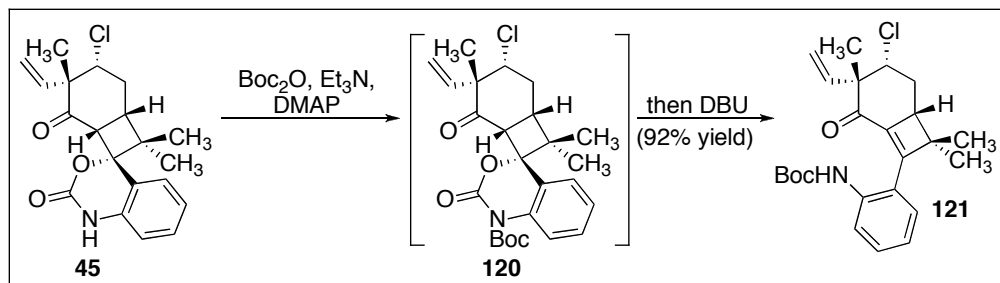
### Preparation of hydroxy quinoline **119**.



To a solution of ketone **45** (2.0 mg, 0.006 mmol) in THF (0.3 mL) was added DBU (1  $\mu$ L, 0.006 mmol) and the reaction was stirred at room temperature for 4 h. The yellow reaction was concentrated under reduced pressure, and DMAP (0.5 mg, 0.004 mmol) followed by  $\text{CH}_2\text{Cl}_2$  (0.4 mL),  $\text{Et}_3\text{N}$  (10.0  $\mu$ L, 0.071 mmol) and  $\text{MeO}_2\text{CCl}$  (5.0  $\mu$ L, 0.065 mmol) were added. Upon addition of the  $\text{CH}_2\text{Cl}_2$ , the yellow color immediately faded. After 10 minutes, TLC indicated that the starting material had been consumed and the reaction was concentrated under reduced pressure and the residue was purified by silica gel chromatography (gradient elution 10  $\rightarrow$  30% EtOAc/Hexanes) to provide **119** (1.0 mg, 64% yield) as a pale yellow oil.

**Hydroxy Quinoline 119:** FTIR (NaCl/thin film) 3068 (w), 2956 (m), 2857 (m), 1664 (s), 1433 (m), 906 (m), 754 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.80 (brs, 1H), 7.45 (m, 2H), 7.36 (d,  $J$  = 8.5 Hz, 1H), 7.18 (t,  $J$  = 7.5 Hz, 1H), 6.85 (dd,  $J$  = 17.0, 10.5, Hz, 1H), 5.73 (t,  $J$  = 7.0 Hz, 1H), 5.23 (d,  $J$  = 17.5 Hz, 1H), 5.11 (d,  $J$  = 10.5 Hz, 1H), 3.20 (t,  $J$  = 7.5 Hz, 1H), 2.67 (m, 2H), 1.91 (s, 3H), 1.55 (s, 3H), 1.46 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  163.8, 160.3, 140.9, 134.0, 132.94, 132.88, 129.8, 129.3, 133.1, 122.4, 117.1, 113.8, 54.0, 48.1, 27.6, 26.6, 21.3, 20.1 (short one  $\text{sp}^2$  hybridized carbon resonance); HRMS (ES $^+$ ) calc'd for  $\text{C}_{19}\text{H}_{22}\text{NO}$   $[\text{M}+\text{H}]^+$  280.1701, found 280.1700. Note: peaks at 0.8 and 1.2 ppm in the  $^1\text{H}$  NMR and at 30 ppm in  $^{13}\text{C}$  NMR are assigned to residual grease from chromatography solvents.

### Preparation of enone 121.

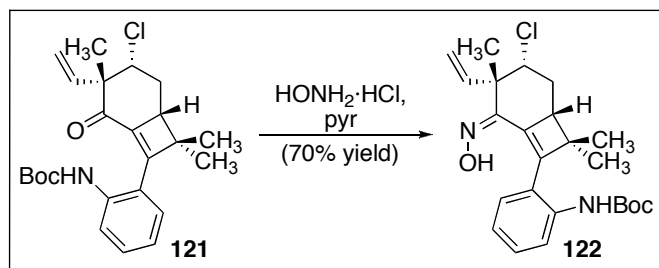


To a stirring suspension of **45** (140 mg, 0.389 mmol) in 3 mL of  $\text{CH}_2\text{Cl}_2$  under  $\text{N}_2$  was added  $(\text{Boc})_2\text{O}$  (100  $\mu$ L, 0.428 mmol) followed by sequential addition of DMAP (2 mg, 0.016 mmol) and  $\text{Et}_3\text{N}$  (0.272 mL, 1.94 mmol). The resulting yellow solution was stirred 30 min, at which time TLC indicated consumption of starting material and DBU (33  $\mu$ L, 0.194 mmol) was added. Stirring was continued at room temperature for 3 h, then the reaction was diluted with  $\text{CH}_2\text{Cl}_2$  and 10 mL of  $\text{H}_2\text{O}$  was added. The aqueous layer was partitioned with a total of 60

mL CH<sub>2</sub>Cl<sub>2</sub>, and the combined CH<sub>2</sub>Cl<sub>2</sub> extracts were washed once with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude orange oil was purified by silica gel chromatography (gradient elution, 0→30% Et<sub>2</sub>O/Hexanes) to give 150 mg (92% yield) of **121** as a yellow oil.

**Enone 121:** FTIR (NaCl/thin film): 3338 (w, br), 2977 (m), 2929 (m), 1725 (s), 1672 (m), 1584 (m), 1523 (m), 1446 (m), 1367 (m), 1247 (m), 1159 (s), 754 (m) cm<sup>-1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.22 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.36 (m, 2H), 7.05 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.06 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.19 (d, *J* = 11.0 Hz, 1H), 4.94 (d, *J* = 17.5 Hz, 1H), 4.31 (dd, *J* = 11.5, 4.0 Hz, 1H), 2.77 (dd, *J* = 11.5, 6.0 Hz, 1H), 2.30 (m, 2H), 1.55 (s, 3H), 1.504 (s, 9H), 1.45 (s, 3H), 1.24 (s, 3H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 197.8, 156.6, 154.2, 138.4, 137.0, 132.8, 130.8, 128.3, 125.0, 124.9, 123.4, 118.1, 79.9, 65.5, 58.7, 49.8, 48.8, 32.9, 28.5, 25.2, 22.8, 21.0; HRMS (ES<sup>+</sup>) calc'd for C<sub>24</sub>H<sub>31</sub>ClNO<sub>3</sub> [M+H]<sup>+</sup> 416.1992, found 416.1992.

### Preparation of oxime 122.

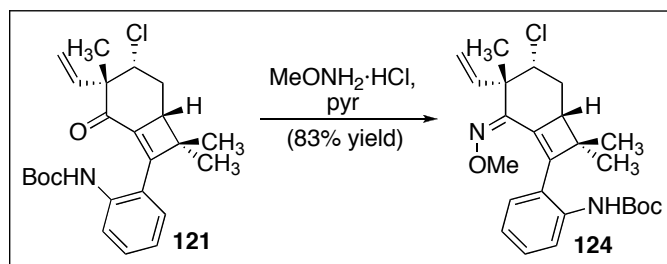


To a glass microwave vessel containing **121** (10 mg, 0.024 mmol) was added HONH<sub>2</sub>·HCl (67.0 mg, 0.962 mmol) followed by 0.5 mL pyridine. The vessel was equipped with a stir bar, sealed, and heated to 65 °C (high irradiation setting) for 2.5 h. The resulting clear solution was diluted with Et<sub>2</sub>O and white solid precipitated. The solid was filtered through celite and washed with a total of 40 mL Et<sub>2</sub>O, and the combined filtrate was concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (gradient elution, 0 → 20% EtOAc/Hexanes) to give 7.0 mg (68% yield) of **122** as a colorless oil.

**Oxime 122:** FTIR (NaCl/thin film) 3397 (m, br), 3310 (m, br), 2978 (m), 1725 (s), 1579 (w), 1514 (s), 1446 (s), 1367 (m), 1244 (m), 1159 (s), 909 (m), 734 (s) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.39 (brs, 1H), 7.26 (m, 1H), 7.16 (s, 1H), 7.00 (d, *J* = 4.5 Hz, 1H), 6.26 (dd, *J* = 18.0, 4.5 Hz, 1H), 5.25 (d, *J* = 10.5 Hz, 1H), 5.06 (d, *J* = 17.5 Hz, 1H), 4.09 (dd, *J* = 8.5, 4.0 Hz, 1H) 2.67 (dd, *J* = 10.0, 7.5 Hz, 1H), 2.32 (ddd, *J* = 13.5, 7.5, 4.0 Hz, 1H),

2.15 (ddd,  $J = 13.5, 9.5, 9.5$  Hz, 1H), 1.48 (s, 9H), 1.43 (s, 3H), 1.42 (s, 3H), 1.16 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ) 154.6, 153.5, 152.0, 139.1, 136.1, 131.3, 128.6, 127.5, 126.2, 122.8, 121.7, 116.7, 80.2, 67.2, 49.9, 49.8, 47.9, 33.2, 28.5, 26.1, 22.2, 20.8; HRMS (ES<sup>+</sup>) calc'd for  $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_3\text{Cl}$   $[\text{M}+\text{H}]^+$  431.2101, found 431.2109.

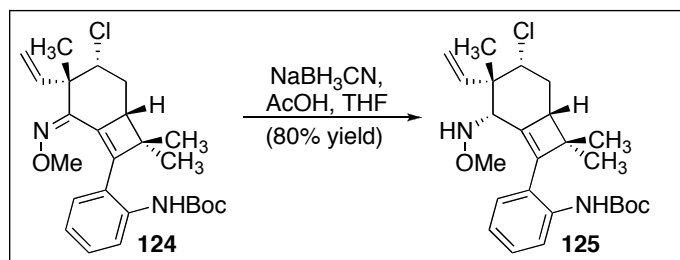
#### Preparation of methyl oxime **124**.



To a glass microwave vessel containing **121** (82.0 mg, 0.197 mmol) was added  $\text{MeONH}_2 \cdot \text{HCl}$  (248.0 mg, 2.96 mmol) followed by 3 mL pyridine. The vessel was equipped with a stir bar, sealed, and heated to 65 °C (high irradiation setting) for 2.5 h. The resulting clear solution was diluted with  $\text{Et}_2\text{O}$  and white solid precipitated. The solid was filtered through celite and washed with a total of 75 mL  $\text{Et}_2\text{O}$ , and the combined filtrate was concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (gradient elution, 0→15%  $\text{Et}_2\text{O}$ /Hexanes) to give 73.0 mg (83% yield) of **124** as a colorless oil.

**Methyl Oxime 124:** FTIR (NaCl/thin film): 3493 (m, br), 3397 (m), 2966 (m), 2934 (m), 1728 (s), 1580 (w), 1517 (s), 1446 (m), 1366 (m), 1241 (m), 1158 (s), 1050 (m), 735 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (d,  $J = 8.0$  Hz, 1H), 7.26 (m, 1H), 7.22 (brs, 1H), 6.99 (m, 2H), 6.26 (dd,  $J = 17.6, 10.8$  Hz, 1H), 5.24 (d,  $J = 11.2$  Hz, 1H), 5.09 (d,  $J = 17.6$  Hz, 1H), 4.09 (dd,  $J = 9.2, 4.0$  Hz, 1H), 3.62 (s, 3H), 2.64 (dd,  $J = 10.0, 7.6$  Hz, 1H), 2.30 (ddd,  $J = 13.2, 7.6, 4.0$  Hz, 1H), 2.13 (ddd,  $J = 13.6, 10.0, 9.6$  Hz, 1H), 1.50 (s, 9H), 1.46 (s, 3H), 1.31 (s, 3H), 1.16 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  153.4, 153.4, 151.1, 139.3, 136.1, 132.2, 128.6, 127.4, 125.8, 122.5, 121.0, 116.6, 80.1, 67.5, 61.7, 49.8, 49.6, 48.1, 33.2, 28.6, 26.2, 22.4, 20.9; HRMS (ES<sup>+</sup>) calc'd for  $\text{C}_{25}\text{H}_{34}\text{ClN}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  445.2273, found 445.2273.

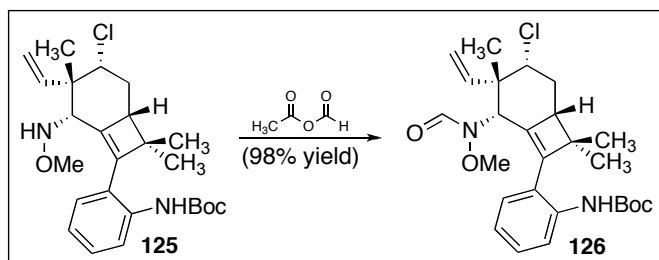
### Preparation of methoxyl amine **125**.



To a solution of **124** (58.0 mg, 0.131 mmol) in 1 mL DCE under  $\text{N}_2$  was added glacial  $\text{AcOH}$  (80.0  $\mu\text{L}$ , 1.31 mmol) followed by  $\text{NaBH}_3\text{CN}$  (83.0 mg, 1.31 mmol). After 1 hr of stirring at room temperature, additional  $\text{NaBH}_3\text{CN}$  (10.0 mg, 0.159 mmol) and  $\text{AcOH}$  (10.0  $\mu\text{L}$ , 0.167 mmol) were added and the mixture was stirred one additional hour. The reaction was quenched with  $\text{H}_2\text{O}$  and diluted with  $\text{EtOAc}$ . The aqueous layer was partitioned with a total of 50 mL  $\text{EtOAc}$  and the combined organic layers were washed once with saturated aqueous  $\text{NaHCO}_3$ , once with brine, and dried over  $\text{MgSO}_4$ . Filtration was followed by removal of the solvent under reduced pressure, and the crude colorless oil was purified by silica gel chromatography (gradient elution, 0 $\rightarrow$ 20%  $\text{Et}_2\text{O}/\text{Hexanes}$ ) to give 47.0 mg (80% yield) of **125** as a white foam. Note: this material is used immediately in the next step as it is unstable to long term storage.

**Methoxyl Amine 125:** FTIR (NaCl/thin film): 3416 (m), 2975 (s), 2952 (s), 2881 (s), 2250 (w), 1728 (s), 1516 (s), 1446 (s), 1367 (m), 1304 (m), 1240 (m), 1160 (s), 1047 (m), 753 (m), 732 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (brs, 1H), 7.43 (brs, 1H), 7.25 (m, 1H), 7.03 (m, 2H), 5.94 (dd,  $J$  = 17.5, 11.0 Hz, 1H), 5.40 (d,  $J$  = 11.0 Hz, 1H), 5.23 (d,  $J$  = 17.5 Hz, 1H), 5.21 (brs, 1H), 3.99 (dd,  $J$  = 12.4 Hz, 1H), 3.60 (s, 1H), 3.21 (s, 1H), 2.40 (dd,  $J$  = 11.5, 6.5, 1H), 2.19 (ddd,  $J$  = 12.0, 6.5, 4.0 Hz, 1H), 2.03 (ddd,  $J$  = 12.0, 12.0, 12.5 Hz, 1H), 1.51 (s, 9H), 1.46 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  153.5, 142.6, 141.2, 136.1, 134.2, 128.3, 128.1, 123.2, 120.1, 80.0, 67.6, 66.5, 60.9, 48.9, 48.7, 34.3, 28.6, 26.5, 22.7, 21.0 (missing 2 carbon resonances); LRMS (ES+) calc'd for  $\text{C}_{25}\text{H}_{36}\text{ClN}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  447.24, found 447.26.

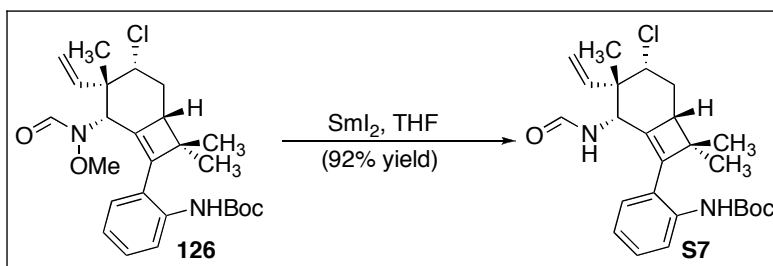
### Preparation of methoxyamide **126**.



To a solution of **125** (54.0 mg, 0.121 mmol) in 6 mL of  $\text{CH}_2\text{Cl}_2$  at under  $\text{N}_2$  was added 100.0  $\mu\text{L}$  of acetic formic anhydride (prepared from heating 0.4 mL  $\text{HCOOH}$  and 0.8 mL of  $(\text{CH}_3\text{CO})_2\text{O}$  to 65  $^\circ\text{C}$  for 45 min under  $\text{N}_2$ ). The resulting solution was stirred for 1 hour at room temperature, then concentrated under reduced pressure. The residue was purified by silica gel chromatography (gradient elution, 0 $\rightarrow$ 30% EtOAc/Hexanes) to give 56.0 mg (98% yield) of **126** as a colorless oil.  $^1\text{H}$  NMR spectra shows two sets of broad peaks for **126** due to rotamers (see attached spectra). The material was generally used immediately in the subsequent reaction.

**Methoxy Amide 126:** FTIR (NaCl/thin film) 3421 (m), 2976 (m), 2877 (m), 1731 (s), 1689 (s), 1516 (s), 1446 (s), 1367 (m), 1236 (m), 1158 (s), 734 (m); LRMS (ES+) calc'd for  $\text{C}_{26}\text{H}_{36}\text{ClN}_2\text{O}_4$  [M+H] 475.24, found 475.47.

### Preparation of formamide **S6**.

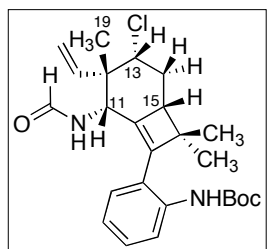


To a solution of **126** (58.0 mg, 0.127 mmol) in 0.5 mL of THF under  $\text{N}_2$  was added  $\text{SmI}_2$  (~0.1 M solution in THF, 3.0 mL, 0.30 mmol) at room temperature. After stirring 15 min, the deep blue solution turned yellow, however TLC indicated remaining starting material. Three additional 3.0 mL portions of  $\text{SmI}_2$  solution (1.20 mmol total, ~10 equivalents) were added over 1 hour, at which time TLC indicated complete conversion. The reaction was quenched by addition of saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  and diluted with EtOAc. The aqueous layer was partitioned with a total of 75 mL of EtOAc, and the combined EtOAc extracts were washed once with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude oil

was purified by silica gel chromatography (gradient elution, 10→30% EtOAc/Hexanes) to give 52.0 mg of **S7** (92% yield) as a colorless oil.

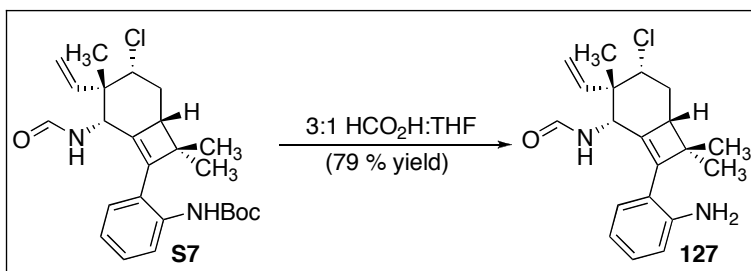
**Formamide S7:** FTIR (NaCl/thin film): 3418 (m), 3311 (w, br), 2967 (m), 2874 (m), 1726 (s), 1691 (s), 1579 (w), 1515 (s), 1445 (m), 1366 (s), 1241 (m), 1158 (s), 1050 (w), 731 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (d,  $J$  = 8.5 Hz, 1H), 7.81 (s, 1H), 7.26 (m, 1H), 6.99 (m, 2H), 6.61 (brs, 1H), 6.03 (dd,  $J$  = 17.5, 11.0 Hz, 1H), 5.51 (dd,  $J$  = 11.0, 1.5 Hz, 1H), 5.26 (dd,  $J$  = 17.5, 1.5 Hz, 1H), 4.71 (d,  $J$  = 9.0 Hz, 1H), 4.04 (dd,  $J$  = 12.5, 4.0 Hz, 1H), 2.50 (ddd,  $J$  = 11.0, 7.0, 1.5 Hz, 1H), 2.24 (ddd,  $J$  = 13.0, 7.0, 11.0 Hz, 1H), 2.08 (ddd,  $J$  = 13.0, 12.5, 11.0 Hz, 1H), 1.51 (s, 9H), 1.27 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  160.8, 153.0, 143.5, 140.9, 136.2, 134.2, 128.8, 128.4, 123.7, 122.8, 121.2, 120.4, 80.8, 66.2, 53.4, 49.5, 49.4, 47.2, 33.8, 28.5, 26.5, 22.7, 21.1; HRMS (ES+) calc'd for  $\text{C}_{25}\text{H}_{34}\text{ClN}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  445.2258, found 445.2270.

The relative stereochemistry of the C11 stereocenter was confirmed by several 1D nOe experiments. Selected nOe's:

	Irradiated Proton	Enhanced Proton
		(% enhancement)
C15	C15	C11 (1.09)
		C14( $\beta$ ) (2.20)
		C13 (2.46)
C13	C13	C11 (3.47)
		C14( $\beta$ ) (2.90)
		C19 (3.00)
C11	C11	C13 (3.51)
		C15 (1.04)
		C19 (3.50)



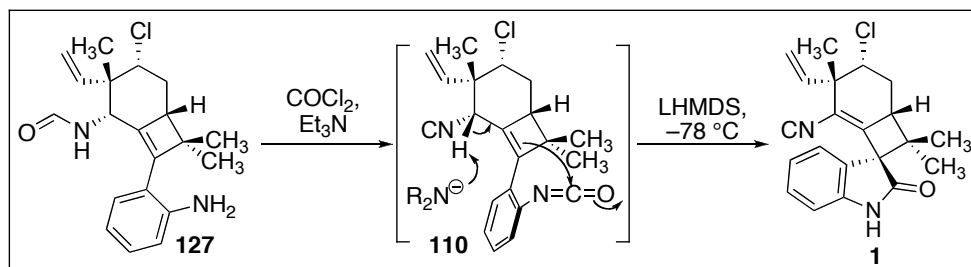
### Preparation of formamide **127**.



To a solution of 22.0 mg of **S7** (0.050 mmol) in 0.2 mL of THF was added 0.8 mL of formic acid. The resulting solution was stirred 6 h at room temperature, after which time the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (gradient elution, 10→50% EtOAc/Hexanes) to give 13.5 mg (79% yield) of **127** as a colorless oil.

**Aniline 127:** FTIR (NaCl/thin film): 3418 (w), 3347 (w, br), 2956 (m), 2922 (m), 2872 (m), 2248 (w), 1686 (s), 1681 (s), 1494 (m), 1450 (m), 1261 (w), 925 (m), 751 (m), 728 (m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (s, 1H), 7.06 (t,  $J = 7.5$  Hz, 1H), 6.98 (d,  $J = 7.5$  Hz, 1H), 6.72 (t,  $J = 7.5$  Hz, 1H), 6.67 (d,  $J = 7.5$  Hz, 1H), 6.09 (brs, 1H), 6.02 (dd,  $J = 17.5, 11.0$  Hz, 1H), 5.44 (d,  $J = 11.0$  Hz, 1H), 5.24 (d,  $J = 17.5$  Hz, 1H), 4.77 (d,  $J = 10.5$  Hz, 1H), 4.04 (dd,  $J = 12.5, 4.0$  Hz, 1H), 3.92 (brs, 2H), 2.44 (dd,  $J = 11.0, 7.0$  Hz, 1H), 2.21 (ddd,  $J = 12.5, 7.0, 4.0$  Hz, 1H), 2.08 (ddd,  $J = 12.5, 12.5, 12.5$  Hz, 1H), 1.27 (s, 6H), 1.25 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  161.3, 143.2, 139.1, 134.4, 128.8, 128.3, 120.7, 119.7, 118.3, 115.5, 66.5, 53.4, 49.8, 49.0, 47.3, 33.7, 26.6, 21.7, 21.6; LRMS (ES<sup>+</sup>) calc'd for  $\text{C}_{20}\text{H}_{26}\text{ClN}_2\text{O}$   $[\text{M}+\text{H}]^+$  345.17, found 345.25.

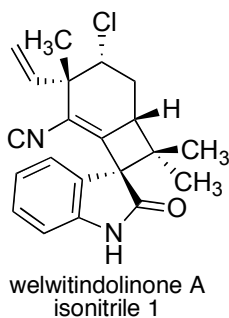
### Preparation of (±)-welwitindolinone A isonitrile (**1**).



A solution of **127** (3.0 mg, 0.0087 mmol) dissolved in 0.3 mL  $\text{CH}_2\text{Cl}_2$  under  $\text{N}_2$  was cooled to 0 °C and  $\text{Et}_3\text{N}$  (8  $\mu\text{L}$ , 0.052 mmol) was added followed by  $\text{COCl}_2$  (20% solution in

toluene, 23.0  $\mu$ L, 0.044 mmol). The reaction was warmed to room temperature, concentrated under reduced pressure, then diluted with dry Et<sub>2</sub>O. The triethylamine salts were removed by filtration under nitrogen, rinsed several times with dry Et<sub>2</sub>O (20 mL total), and the filtrate was concentrated under reduced pressure. The residue was azeotroped with benzene (2 x 1 mL) and dried *in vacuo* for 3 h. Meanwhile, a separate flame dried flask was charged with 90.0 mg of solid LHMDS in a glovebox. The flask was capped with a septum, removed from the glovebox, and 0.50 mL of dry THF was added under N<sub>2</sub> to give a 1.08 M solution. The crude isocyanate was dissolved in dry THF while under N<sub>2</sub>, cooled to  $-78$  °C and LHMDS (44.0  $\mu$ L, 0.044 mmol) was added. After 15 min, the reaction was quenched with water and diluted with EtOAc. The aqueous layer was partitioned several times with EtOAc (30 mL), and the combined EtOAc extracts were dried over MgSO<sub>4</sub>. Filtration was followed by removal of the solvent under reduced pressure, and the crude residue was purified by silica gel chromatography (gradient elution, 0 $\rightarrow$ 20% Et<sub>2</sub>O/benzene) to give 1.4 mg (47% yield) of **1** as a yellow oil.

**Welwitindolinone A Isonitrile (1):** FTIR (NaCl/thin film): 3269 (s, br), 2959 (m), 2925 (m), 2854 (w), 2106 (m), 1708 (s), 1621 (m), 1469 (m), 1369 (w), 1326 (w), 1262 (w), 1207 (w), 1115 (w), 755 (m), 746 (m), 711 (m) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  7.39 (brs, 1H), 7.29 (dt,  $J$  = 7.5, 1.0 Hz, 1H), 7.23 (d,  $J$  = 7.5 Hz, 1H), 7.06 (dt,  $J$  = 7.5, 0.5 Hz, 1H), 6.91 (d,  $J$  = 8.0 Hz, 1H), 5.94 (dd,  $J$  = 17.5, 10.5 Hz, 1H), 5.46 (d,  $J$  = 10.5 Hz, 1H), 5.31 (d,  $J$  = 16.5 Hz, 1H), 4.03 (dd,  $J$  = 12.5, 3.0, 1H), 3.59 (dd,  $J$  = 10.5, 6.5 Hz, 1H), 2.03 (ddd,  $J$  = 12.0, 6.5, 3.0 Hz, 1H), 1.92 (ddd,  $J$  = 12.5, 12.5, 10.5 Hz, 1H); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  175.9, 167.9, 141.9, 138.33, 138.28, 129.7, 127.6, 123.3, 122.1, 118.3, 110.4, 65.5, 64.5, 48.3, 47.9, 47.4, 29.3, 23.7, 21.63, 21.57 (missing two carbon resonances, C11 and C10); HRMS (ES<sup>+</sup>) calc'd for C<sub>21</sub>H<sub>22</sub>ClN<sub>2</sub>O [M+H]<sup>+</sup> 353.1421, found 353.1405;  $m/z$  353.1405/355.1387, 3:1 [M + H]<sup>+</sup>, 317.1649 [M-Cl]<sup>+</sup>.



Reported	Observed
7.62, 7.50, brs, 1H (N-H)	7.39, brs, 1H (N-H)
7.29, td, 7.7/1.2, 1H	7.29, dt, 7.5/1.0, 1H
7.24, ddd, 7.7/1.2/0.6, 1H	7.23, d, 7.5, 1H
7.06, td, 7.7/1.2, 1H	7.06, dt, 7.5/0.5, 1H
6.92, ddd, 7.7/1.2/0.6, 1H	6.91, d, 8.0, 1H
5.99, dd, 17.3/10.8, 1H	5.94, dd, 17.5/10.5, 1H*
5.46, dt, 10.8/0.5, 1H	5.46, d, 10.5, 1H
5.32, dd, 17.3/0.5, 1H	5.31, d, 17.5, 1H
4.04, dd, 12.5/3.2, 1H	4.03, dd, 12.5/3.0, 1H
3.60, dd, 10.6/7.0, 1H	3.59, dd, 10.5/6.5, 1H
2.03, ddd, 12.5/7.0/3.2, 1H	2.03, ddd, 12.0/6.5/3.0, 1H
1.92, td, 12.5/10.6, 1H	1.92, ddd, 12.5/12.5/10.5, 1H
1.43, s, 3H	1.43, s, 3H
1.26, s, 3H	1.26, s, 3H
1.19, s, 3H	1.19, s, 3H

\*Baran and Richter report a similar value.<sup>2</sup>

References:

1. Gross, M. L.; Blank, D. H.; Welch, W. M., *J. Org. Chem.* **1993**, *58*, 2104-2109.
2. Baran, P. S., Richter, J.M., *J. Am. Chem. Soc.* **2005**, *127*, 15394-15396.